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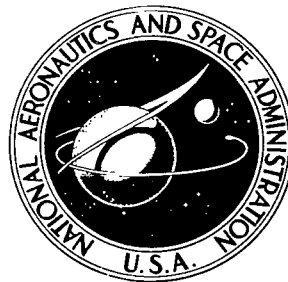
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PERCEPTION OF THE RESPIRATORY MEDIUM AND GAS PREFERENCE IN MAN AND ANIMALS

by I. S. Breslav

PERCEPTION OF THE RESPIRATORY MEDIUM AND GAS PREFERENCE

IN MAN AND ANIMALS

I. S. Breslav

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SUMMARY

Wide application of artificial respiratory mixtures in clinical practice, in diving, in high altitude and space flights has attracted attention to the effects of altered gas media on the human body.

There are opinions in physiology and aviation medicine that a man is unable to determine by his conscious perception the suitability of gaseous mixtures for breathing, and sometimes cannot detect changes of inhaled air dangerous to life. However, this opinion has not been verified experimentally.

In order to study this question, the author elaborated and employed the method of active choice of preferred respiratory mixtures by man and animals (gas preference).

Experimental animals (laboratory and wild rodents) were placed into a specially constructed device where the gradient of some gas was maintained. The animal could choose the preferable composition of gas medium by freely moving within the device. In human experiments, the subjects (healthy young men and women) breathed through a mask different gaseous mixtures in turn, and actively chose one of them guided by their perception.

It was found that both animals and man avoided gas media where either oxygen content was decreased to 10-12% and less, or carbon dioxide content was increased to 2.5-3% and more. A sharply negative response was shown to the mixture having a moderate decrease of oxygen percentage combined with a small amount of CO_2. Man's ability to detect hypoxic and hypercapnic media increased when time of inhalation of the offered mixtures was prolonged. Analysis of the experimental data suggests that avoidance response towards these gas mixtures is related with the corresponding hypoxic and/or hypercapnic shift in the body

and partly is caused by increased work of breathing due to hyperventilation.

When common (nitrogen-oxygen) and helium-oxygen mixtures were offered, with other conditions unchanged, man and animals chose the latter. This fact can be explained by reduced resistance to the turbulent gaseous stream in the respiratory tract when breathing helium mixtures.

Under the condition of a fixed breathing regime (deliberately maintained constant ventilation), the subject's ability to detect alterations in gas medium composition increased significantly. If a higher level of ventilation was offered, the subject preferred to breathe not common air, but such mixtures which were adequate for forced hyperventilation.

Denervation of sinocarotid zones in rats resulted in reduction of behavioral reaction to hypoxic and (to a lesser extent) hypercapnic media. Therefore, arterial chemoreceptors are the part of the afferent path for gas preference reaction.

Repeated exposure to the same gaseous mixture fixed the response. In man, ability to differentiate such a mixture from the air was perfected. Only the rodents living under natural conditions in deep holes revealed a lack of reactions towards hypoxic and hypercapnic media. Similar but transient decrease of hypoxic avoidance was displayed in rats which were kept in an oxygen-poor atmosphere for a prolonged time.

Man more willingly breathed hyperoxic mixtures or pure oxygen than common air when ambient oxygen partial pressure was reduced (exposure in a decompression chamber at certain degrees of air rarification, a stay in mountains, etc.). At the end of monthly acclimatization in the mountains, this positive response of the subjects to oxygen disappeared.

Thus active choice of respiratory media reveals adaptation (congenital or acquired) of man and animals towards habitual atmospheric composition. Gas preference can be used as one of the criteria of physiological adequacy of

certain gas mixtures for the investigation of optimal artificial atmosphere under different conditions of the organism's activity.

As was shown, man is quite capable of detecting respiratory media alterations by means of his conscious perception. It seems that further study in this area and its possible perfection are of great theoretical and practical interest.

PERCEPTION OF THE RESPIRATORY MEDIUM
AND GAS PREFERENCE IN MAN AND ANIMALS

I. S. BRESLAV

ABSTRACT. The book is devoted to the problem of the perception of the respiratory medium and to the behavioral responses of the organism to its composition changes.

The author developed and employed a method of active choice of preferred gas mixtures (gas preference) for investigations in animals and in man. Particularly, man's ability to detect changes of inspired air gas composition was determined. A physiological analysis of the active choice was   ses was performed. The relation between these responses and "tuning" of the organism with a certain composition of the atmosphere was demonstrated. It was shown that the gas preference method can be applied to the evaluation of physiological adequacy of different respiratory mixtures.

FOREWORD

The physiology of respiration is at present experiencing a complicated   /5*
period in its development. On one hand, the most intimate processes of pulmonary
gas exchange and mechanics of the respiratory act are being successfully investi-
gated. The regulation of respiration has already been so well studied that the
amount of ventilator response in any combinations of hypoxic and hypercapnic sti-
muli can be predicted. However, on the other hand, life makes demands on this
field of physiology which cause it to take up again problems that would appear
to be already solved. It is not without reason that the overwhelming majority
of works on the physiology of respiration appears in publications of applied
sciences. More and more often, man must change the usual respiratory medium --
atmospheric air -- to an artificial one. In the respiratory and blood-circula-
tion disease clinic, in surgery and anesthesiology, inhalations of various gas

* Numbers in the margin indicate pagination in the original foreign text.

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mixtures are widely applied. High-altitude and space flights and descents of man under water are both concerned with periods in an artificial atmosphere.

The author of this study has approached the problem of the physiological influence of an altered respiratory medium in an original manner. He has developed a principally new method which permits the organism to choose independently the preferred atmospheric composition -- the gas preference method.

The author has discovered the ability of animals and man to distinguish /6 changes in the composition of the respiratory medium. This has great value, not only on the general biological plane, but also in practice. In particular, the development of this ability in man (up until now, hardly studied at all) might be used in selecting and training fliers and astronauts, and also in evaluating safety control in high-altitude and space flights.

Active choice, as the data presented in the monograph show, is a generalized integral index of the physiological adequacy of a gas medium for animals and man. This helps to clarify the optimum composition of respiration mixtures for a physiological condition of an organism, and under conditions of a long period in an altered gas medium -- to evaluate the possibility of adapting to such a medium.

It is highly probable that the gas preference method will find application in research in selecting therapeutic gas mixtures for various diseases, recommending the composition of an artificial atmosphere for enclosed habitations under ground, under water, and in outer space, etc.

A critical outline is given in the monograph of current research on receptor instruments, which provide adequate organism response in an altered respiratory medium. Incidentally, the appearance of such a survey in Russian is long overdue.

This work undoubtedly enlarges the arsenal of research methods and deepens our concepts in the field of respiration regulation. Thus it will be of special interest for doctors and physiologists.

Leningrad, January, 1968

Professor A. G. Zhironkin
Doctor of Medical Science
Editor

INTRODUCTION

The higher animals and man have refined analyzer systems which contribute <u>/7</u> to the continuous adaptation of the functions of the organism to changing conditions of external and internal environment. Appropriate sensitive instruments ensure responses to the smallest fluctuations of temperature, light and other factors. In particular, the olfactory receptor, which I. P. Pavlov included together with the gustatory receptor in the concept of chemical analyzer, can detect the most insignificant admixture in inhaled air. Suffice it to say that man has the ability to detect by smell the presence of trinitrobutyltoluene in a concentration of $5 \cdot 10^{-13}$ grams in 100 ml of air (Bronshteyn. 1950).

At the same time, our chemical analyzer is apparently "deaf" to the content of the basic components of the atmosphere itself. Textbooks usually say that oxygen, nitrogen and inert gases are "ordorless and tasteless". Carbon dioxide is an exception. However, the unique "smell" of carbon dioxide is only detected in high concentrations, which are never met under ordinary circumstances.

And at the same time precise responses of respiration and other systems to relatively small changes of the partial pressure of oxygen and carbon dioxide in inhaled air have been well researched.

An explanation of the physiological meaning of the contradiction between an apparent inability of the organism to perceive immediately the content of an inhaled gas mixture and the presence of mechanisms of adaptation to changes in the content of oxygen and carbon dioxide in the atmosphere would, in our opinion, shed light on some, as yet not fully clear, aspects of respiration regulation.

The ability to distinguish the gas content in an inhaled medium can be <u>/8</u> not only of theoretical, but also of practical importance. The history of aeronautics and mountaineering tells of many instances of the tragic death of

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people who were unable to notice a threatening lowering of oxygen partial pressure in the atmosphere. It is true that the development of life support systems and methods of gas medium control have greatly reduced this danger. However, man's rapid conquest of outer space and the ocean depths makes this problem urgent again. Astronauts, and frequently also aquanauts, must breathe an artificial gas mixture, the content of which can change unexpectedly for various reasons. Could a man, not consulting the corresponding instruments, distinguish shifts in the content of an inhaled mixture which are essential to him and take necessary measures, in the same way that a pilot, for example, using his own senses, can adjust the temperature conditions in the cockpit? This question is also of great importance since the composition of an artificial atmosphere will probably differ from ordinary air.

The immediate value of this research is also in the explanation of the question of man's and animals' ability to distinguish changes in the composition of basic components of the respiratory medium. Exactly what is meant here by the term "distinction" must be more accurately defined. Strictly speaking, an organism perceives a change of any parameter of the medium each time there is a response of some physiological function to that change. By way of illustration, if in the respiration of a mixture containing 0.25% CO_2, an increase in pulmonary ventilation is noticed in man, then the organism is already distinguishing such a concentration.

But in this work we are using the term "distinction" in a narrower sense-- as the ability of man to give a verbal report about his sensations by which he determines changes in the composition of the respiratory medium. In animals another, although incomplete, analogy with these distinctions presents general behaviour response in the form of active movement in space, caused by localized changes in the gas composition of the atmosphere.

To research similar responses in various respiratory media, we have developed a method of active choice of preferred gas mixtures -- gas preference.

Under conditions of free movement in space, the organism selects a zone which is physiologically optimum according to several indices. Such responses of free choice have been given the name of preferences. The choice of animals of points of preferred temperatures -- thermal preference -- can be observed (Herter, 1924; Kalabukhov, 1939, and many others). Photopreference has been researched -- the choice of physiologically adequate illumination zones (Hooker, 1911, cited by Mrosovsky and Carr, 1967, and others). Also related /9 to preference is discrimination displayed by animals and by man concerning forms of food and drink (Kassil', 1964, 1969; Kassil', Ugolev and Chernigovskiy, 1964 and others).

The gas preference method consists of recording the preferences which an organism shows for one respiratory medium in comparision with others. Gas preference in animals is revealed in the form of their active movement under conditions of a spatial gradient of gas concentration, and in man in the form of a substantiated verbal report of the choice of one of the respiratory mixtures offered. As will be shown, gas preference reflects an integral response to changes of the gas composition of a medium and can properly serve as a criterion of an organism's ability to distinguish these changes.

We thought it important first of all to clarify the following problems:

1) exactly what changes in the composition of the gas medium can be distinguished by animals and man;

2) what is the mechanism of gas preferences responses, primarily their receptor element;

3) what is the biological role of these responses and what factors determine an organism's choice of a respiratory mixture.

EVALUATION OF RESPIRATION AND THE GASEOUS ENVIRONMENT

Animals' reception of the gas medium and responses to a change in its composition are closely connected with the process by which gaseous exchange occurs between an organism and the surrounding medium. In proportion to the complexity of the respiration function, these responses not only are perfected, but are fundamentally changed. So far very little is known about the choice of the respiratory medium by animals at various stages of the evolutionary scale (see survey: Zhironkin and Breslav, 1968).

Invertebrates

In unicellular animals living in water, gaseous exchange occurs through the surface of their bodies; therefore, the only means of regulating respiration here is movement in the water. Each form chooses the zone not only of proper temperature and salt composition of the water, but also of oxygenation adequate for itself. Thus, the distribution of zooplankton at certain stages reflects the gas saturation of various layers of the water and current. One of J. Haldane's colleagues (Bles, 1929; cited by Haldane and Priestley, 1935) described the behavior of the shell amoeba (Arcella discoides). When it is in a weakly oxygenated medium, it produces in its cytoplasm vacuoles of almost pure oxygen which make it lighter, and it floats up to a layer of water more saturated with this gas.

The expressed preference concerning oxygen content can also be observed in more highly organized invertebrates. One form of shrimp (Penaeus japonicus) usually buries itself in sand, but when the oxygen concentration in the medium

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falls to a certain level, the animal protrudes from or completely comes out of the sand (Egusa and Yamamoto, 1961).

Klinger (1963), observing the movement of nematodes under experimental conditions, recorded positive taxis of round worms in relation to a source of carbon dioxide, which served as a reference point for them in the search for food. A similar phenomenon is also encountered in several insects, (Prosimulium decematriculatum, Simulium euryadminiculum, S. aureum; Fallis and Smith, 1964). In other forms of insects, carbon dioxide preference is connected with choosing a suitable place for oviposition (Orthosoma brunneum) (Palm and Beckel, 1964). Chemoreceptors in the weevil larva Otiorrynchus sulcatus,used for orientation of carbon dioxide concentration,were discovered in the end joints of the jaw feelers (Klinger, 1966).

The preference that many invertebrates have concerning carbon dioxide can hardly be coincidental. It is known that termites spend almost all their lives in a medium carefully isolated from outside air and saturated with moisture, where the carbon dioxide concentration approaches 15 - 18% (Halifman, 1962). It is possible that the atmosphere of the Earth had a similar composition in earlier geological eras (Sokolov, 1966) when termites were also widely distributed, and they have been preserved now as living fossils.

It occurs to us that a study of gas preference of organisms on various levels of the evolutionary scale could shed light on several, as yet unresolved, questions concerning changes occurring in the composition of the atmosphere during the development of life on our planet (Gilbert, 1968).

Fish

Although fish have a comparatively complex system of respiration (gills and,in several varieties, cutaneous and intestinal respiration,) they do not possess a developed mechanism for regulating this function. Their respiratory movement increases only in an insignificant degree with an insufficiency of oxygen and an excess of carbon dioxide. (Babak, 1907; Voskoboynikov and

Balabay, 1935 and others). At the same time, fish must discharge through their gills a relatively large quantity of water to extract the oxygen. (Dejours et al., 1968).

The choice of a water medium which contains a certain concentration of dissolved oxygen is the primary means of meeting the gaseous exchange requirement in these animals. Within the optimum zone selected by the fish, fluctuations of oxygen concentration do not influence the gaseous exchange of the fish in question (Privol'nev, 1947) and normal incubation of their embryos occurs (Bishai, 1960). On this basis a functional-respiration theory of fish migration is suggested. If the concentration of oxygen in a medium falls below /12 the zone of oxygen adaptation characteristic for a particular population, the fish cannot compensate for this decrease by intensified respiratory movement and begin to search for a place with more highly oxygenated water, especially in the period of spawning migration when gaseous exchange in the organism increases (Privol'nev, 1948).

Various kinds of fish select water which has a different degree of oxygenation. Some fish prefer cold water where there is more dissolved oxygen and lay their eggs in fast running, but consequently well-oxygenated streams (Puchkov, 1954). Sea fish are especially exacting with regard to the gas condition of the water. The regular distribution of fish in various sea currents has a direct practical importance in forecasting concentrations of commercial varieties. (Ardov, 1964). The "oxygen threshold" of fish can be altered as a result of long periods in water of higher or lower oxygenation. (Puchkov, 1954).

Thus, fish possess a clearly expressed gas preference which serves essentially as a direct mechanism for respiration regulation. This phenomenon has also been studied under experimental conditions. A number of authors have noted natural migration of fish in an artificially produced spatial gradient of oxygen content. (Jones, 1947, cited by Sommers, 1962; Whitmore et al, 1960, cited by Sommers, 1962). By reinforcing the active movement of small goldfish by offering oxygenated water, Sommers (1962) noted an adequate motor

response of the experimental species. The author defined this response as the ability to regulate the respiratory medium by means of acquired behavior.

Where are the receptor fields which enable fish to perceive the gas composition of a water medium? There is basis to assume that they are the branchiate receptacles which come in direct contact with the water flowing through the gills and serve as chemosensitive zones (Sepp, 1949; Hughes and Shelton, 1962). The receptor endings of branchiate arms of the vagus nerve located here generally play an important role in respiration regulation of fish, which are known to be sensitive to a deficiency of oxygen and insensitive to an excess of carbonic acid. (Babak, 1907; Kravchinskiy, 1945; Krogh, 1959; Serbenyuk, 1968). As indicators of the oxygen content in the surrounding water medium, the branchiate receptors can be considered as homologues of the small carotenoid coils in terrestial vertebrates (Chernigovskiy, 1960).

On the whole, there has been very little research done on behavior responses of fish to the gas composition of a medium. Even the recently published collection Povedeniye i retseptssi ryb (Behavior and Reception of Fish) (1967) did not contain one work which concerns this question.

The peculiar behavior of fish which breathe in two ways is interesting. These are forms transitional to terrestial vertebrates. In the water, these /13 animals can exist for some time by gill respiration, but for full gaseous exchange they must come to the surface periodically to gather a portion of air into their primitive lungs. An appropriate chemoreceptor impulse probably serves as the stimulus to float up. The existence of receptors which sense oxygen and carbon dioxide in the surrounding medium is demonstrated in dual-breathing fish, but their localization is not yet known. (Jesse et al., 1967).

Terrestial Vertebrates

With the transition to an air medium and to exclusively pulmonary respiration, the entire "respiratory behavior" of the organism changes qualitatively.

The composition of the lower layers of the atmosphere is almost identical over the whole planet. At sea level, out of a general barometric pressure of 760 mm Hg., the partial pressure of oxygen is, on the average, about 159 mm Hg, fluctuating with varying meteorological conditions (pressure, temperature, humidity) from 140 to 163 mm Hg. (Orlov, 1959). The partial pressure of carbon dioxide does not usually reach 1 mm Hg. The rest of the air comprises nitrogen with a small admixture of hydrogen and inert gases, basically argon, and water vapor.

Because of the spatial uniformity of the atmosphere, the emphasis on respiration in terrestial animals is transferred from adaptation to the external medium to the regulation of gaseous conditions of the internal medium. An organism's gaseous exchange varies mainly in connection with muscular activity; to a lesser degree, it is influenced by temperature and other factors. The higher animals have an exceptionally perfected apparatus to control the interior medium most delicately. It is sufficient to recall with what precision the constancy of gas pressure is maintained in the alveolar air to blood.

Since a choice of the interior gas medium is no longer demanded, the motor apparatus is set free from a given function. In this connection, as is known, under natural conditions terrestial vertebrates do not develop a gas preference. But doesn't this indicate that the higher animals are deprived of the ability to respond to changes in gas medium composition? Not at all. We know that the apparatus for respiration regulation and blood circulation in the higher vertebrates is also very sensitive to the oxygen and carbon dioxide content in inhaled air. Therefore, these animals also possess receptor apparatus which enables them to distinguish the composition of the respiration medium. Perhaps only the uniformity of the composition of this medium under natural conditions keeps us from observing behavior responses similar to those described in lower organisms, mainly water creatures.

But the possibility of gas preference in higher animals and man has hardly /14 been studied at all. This can be explained first of all by methodological reasons. A noticeable spatial drop of gas concentration is not found in the

atmosphere, and it is difficult to make such a gradient artificially because of the rapid displacement of gases. Therefore, up until now, selection of a preferred gas medium, in the literal sense, has not been described for vertebrate animals. We have attempted to overcome these methodological difficulties, taking notice of certain approaches to the problem used by a number of researchers.

TECHNIQUES OF GAS PREFERENCE STUDY

Animal Experiments

Theoretically, gas preference in animals can be discovered using various methods.

In the research cited on lower animals, simple observations were made of the behavior of experimental objects under conditions of a naturally or artificially constructed oxygen or carbon dioxide gradient (Jones, 1947; cited by Sommers, 1962a; Klinger, 1963). But it is difficult to maintain a gas gradient in an air medium, and visual analysis of animal reactions under free behavior conditions is unexact. Sommers used a more complex methodological process. He developed specialized motor responses in experimental animals. A conditioned reflex was developed in tortoises, to the pressure of a lever controlling the air supply (Sommers, 1963a). In experiments with rats, a hypercapnic mixture was supplied, and the animals were trained to press a special tube or disc to stop the entry of this mixture (Sommers, 1962b). Weinstein (1967) used an analogous method in experiments with doves.

However, even this research method is faulty. Responses to a gas medium are registered by an artificially developed motor act, which complicates the experiment and interpretation of its results.

At one time Herter (1934) in research on temperature preference constructed a special thermogradient instrument -- a long chamber along which a drop in temperature was produced. In such an instrument the animal could choose the temperature he preferred.

We used an analogous principle as the basis of our research with small animals. But it is considerably more difficult to construct a gradient of· gas content than it is a temperature gradient. It proved to be necessary to construct a special arrangement of continuous gas supply for this purpose. /15

The principal part of the gas gradient instrument (Breslav and Il'nitskiy, 1964; Breslav, 1965a) which we built (Figure 1 and 2) is a narrow chamber divided into 10 - 20 sections by partitions in which there were openings. In Figure 1 the partitions are seen in the mirror mounted on the chamber. The dimensions of the sections and openings depend on the kind of animals used in the experiments. In the roof of the chamber there is a door to put in the animals. The chamber lies half-way along a transverse axis (Figure 2, 0) and when the animal moves there is a small vibration in the vertical plane. These vibrations are transmitted by means of a gear transmission and double-arm lever to a stylus which registers all movements of the animal in the chamber on kymographic tape. Contacts $(K_1$ and $K_2)$ are located under both ends of the chamber. Each is closed by the least slant of the chamber. The contact turns on a pulse counter circuit $(C_1$ and $C_2)$, which fixes, with the help of an interceptor in the same circuit, the time period (n) the animal is in the corresponding half of the chamber.·

To maintain the gradient of gas composition, there are pipes in the end walls of the chamber through which gases or gas mixtures are continuously supplied from tanks during the experiment. Gradually mixing, these gases constantly maintain a linear drop of the medium composition between sections of the chamber. Naturally, the maximum difference in gas composition occurs between the end sections. After partial mixing, the gas leaves the chamber through pipes in the front walls opposite each section. /16

The mixtures can be prepared beforehand in the tanks themselves, or they can be produced from gases from two or more tanks along the supply route in each end pipe, (Figure 2, 1, 2). To create the necessary gradient in the chamber, a specific delivery speed is set for the gases in the end pipes (6) of the chamber (7) using valves (4) controlled by floating rotameters (3,5).
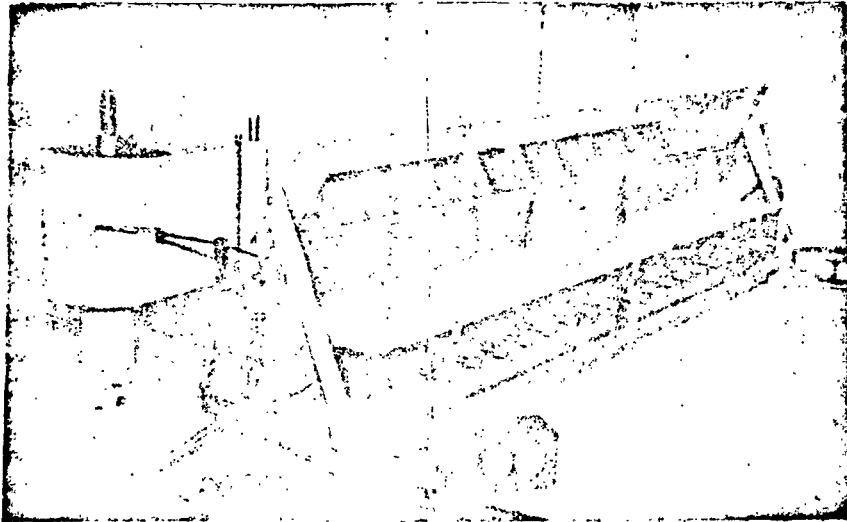
Figure 1.　A gas gradient instrument for small
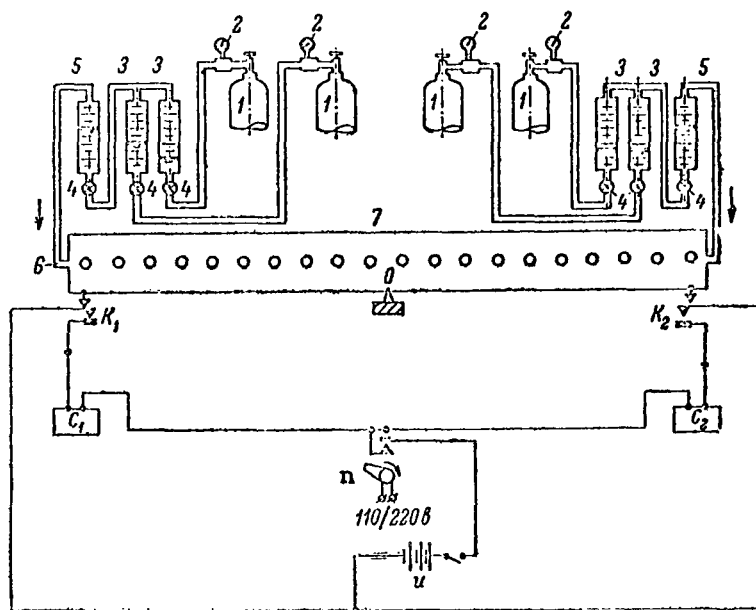animals.　General view.

Figure 2.　A diagram of the gas supply in the chamber
of the gas gradient instrument and the recording of
the behavior of the animal.　Explanation in the text.

The gas flows which pass through both the left and the right end pipes
(indicated in the illustration by arrows) must be low and equal between them.
Otherwise, in the experiments the animals could respond not only to the
composition, but also to the different speeds in the movement of the gas
mixtures in various parts of the chamber. Other necessary conditions are
uniformity of temperature and illumination along the whole length of the
chamber, and the absence of foreign irritants which could influence the behav-
ior of the animal during the experiment. Regarding this last case, the front
wall of the chamber is covered with dark lacquer. The mirror we mentioned
permits the behavior of the animal to be observed visually.

In our experiments, in the first minutes the animal usually made a number   /17
of orientation runs along the chamber, after which he usually chose one of
the ends, where he stayed until the completion of exposure. The normal length
of the experiment was from 10 to 30 minutes.

In the experiments, as a rule, we used the most simple strains: white mice
CC 57 (2 - 3 months old) and white Vistar rats (3 - 4 months old). Special ser-
ies were conducted with rats of various ages and also with several types of
wild rodents.

Human Experiments

In the literature available to us, there was no research specially dedi-
cated to human gas preference. An exception might be one work (Bartlett and
Hertz, 1962) whose purpose was quite limited: men alternately breathed air
and pure oxygen through a mask to determine if the subjects could distinguish
one of these respiratory media from the other.

In our experiments we used the principle of an active choice of gas
mixtures breathed through a mask with a verbal characterization of each mixture
by the subject.

Determining gas preference was not the only aim in human observation. The dynamics of external respiration and several other physiological indices for the inhalation of various gas mixtures were determined. This was necessary for physiological analysis of the responses observed in the subjects and for the choice of respiratory media.

To conduct these kinds of complex experiments, it was necessary to use an apparatus which could report accurate computations of the dynamics of pulmonary ventilation in the respiration of various mixtures and which could also provide quick and convenient switching of the subject from one mixture to another. The composition of each of the inhaled mixtures had to remain constant during the course of the experiment. With this aim, we constructed jointly with B. N. Volkov and V. M. Mityushov (Breslav et. al., 1969) an apparatus, based on a hydraulic spirograph, which would provide respiration with gas mixtures not in a closed system (as in the usual spirograph), but in a circulating system with an automatic flow of inhaled mixtures through gas counters. This method gives a constant concentration of each of the respiratory mixtures and an accurate recording of a volume of respiration per minute. Change from one mixture to another is accomplished using electric switches, instantaneously, without disturbing the continuity of the recording.

The principle of the operation of the apparatus (Figure 3) is as follows. /18 The subject breathes through a mask (1). The inhalation comes from the spirograph cylinder (2), and the exhaled air emerges through a valve (3). During exhalation, a pneumatic mercury pressure switch (4) connected with the mask, and a relay system (the electric circuit is not shown) close the corresponding electromagnetic inhalation valve (5) and turn on the automatic flow of the mixture to the spirograph from the gas tank (6). The mixture is admitted, since the electromagnetic valve (7) is opened and passes through the gas counter (8). The power supply circuit of the valve is opened by a certain position of the writing mechanism with a sliding contact (9), which is connected with the spirograph cylinder. Consequently this is filled exactly to its original level, at which the next respiration cycle begins. Two or more of these spirograph lines can operate in the apparatus, each being connected with
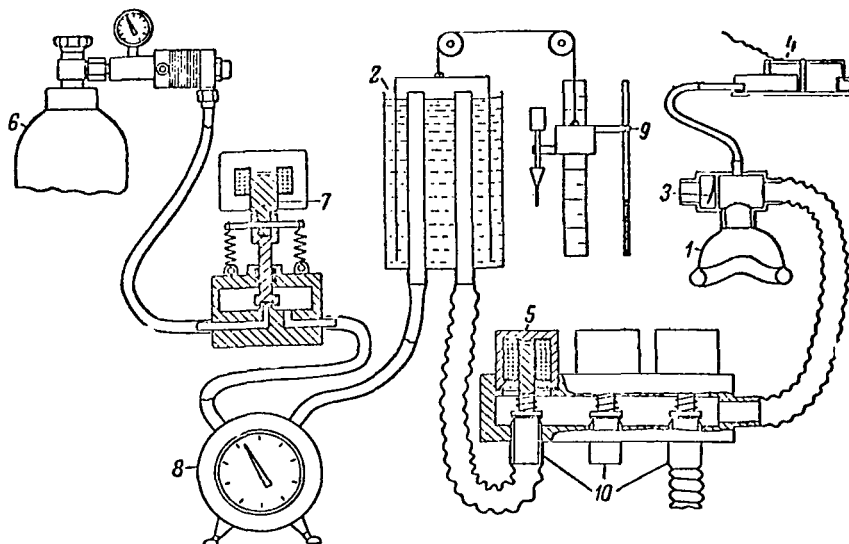
Figure 3. Diagram of the spirograph line. Explanation
in the text.

a separate gas tank and inhalation valve [three such valves (10) are depicted
in the diagram] which record the respiration of a specific gas mixture. The
subject changes from one respiration mixture to another by means of a button
switch placed in a panel.

During the experiment, the subject sat quietly at the panel (Figure 4)
in a comfortable chair and breathed through a small mask which covered only   /19
the nose area. This provided nasal respiration, which is the most physiolog-
ical respiration with little (about 15 ml) additional dead space.

During the course of the experiment, besides the respiration curve, a
record of the oxygenation of the subject's blood was also kept on the spiro-
graph tape (using selsyns which duplicated the readings on the oxyhemograph
0-36M), as well as his pulse (by a specially modified pulse tachometer).

The dynamics of the composition of the exhaled air were continuously re-
corded by a quick-response gas analyzer GUM-2 and an oxygen analyzer MMG-7.

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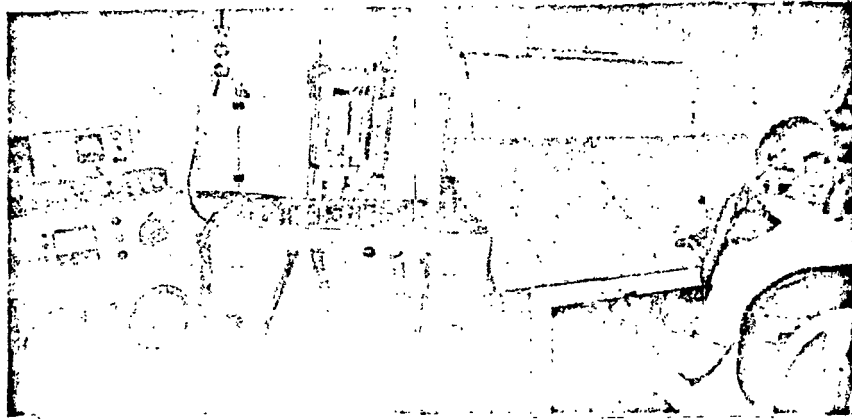
Figure 4. Apparatus for studying human gas preference.
The subject in the mask is at the panel which switches
the respiratory mixtures. At the left of the panel —
the unit which automatically supplies gas mixtures and
records parameters of respiration and pulse.

Calculation of the composition of alveolar air as well as alveolar ventilation
was performed according to the last fraction of exhalation, using the equations
of Fenn and Rahn (Fenn, Rahn, Otis, 1946).

Course of the Experiment. Before the experiment, the subject rested for
20 minutes. The experiment was begun with five minutes of breathing room
air, after which began a "period of prescribed respiration", which served as
a physiological index in the inhalation of the gas mixtures used in the
experiment and to first acquaint the man with the mixture. In each experiment
two mixtures were presented. The subject breathed the first of them for 5, 10,
and 15 minutes, and then breathed the other mixture for the same length of
time. The mixtures were changed by commands from a magnetic tape recorder.
We will cite the physiological characteristics recorded in the last minute of
respiration of one or other of the mixtures as characteristic.

A period of free choice of 10 or 15 minutes followed the prescribed /20
respiration. The subject could be switched from mixture to mixture, as he
desired, until he selected one of them on the basis of his own sensations. At
the end of the experiment, he gave a verbal report to characterize his
sensations in breathing each of the gas mixtures presented.

The composition of the respiratory mixtures was not made known to the subject. The order in which the different mixtures were used in the experiments and the location of the buttons which the subject used to switch from one mixture to the other were carefully randomized, i.e., they were varied in a consciously random order to avoid the influence of attendant factors (formation of conditioned association with the sequence of mixtures or the location of the switch while breathing a certain mixture) on the man's distinguishing and selecting of mixtures.

General Principles of Gas Preference Evaluation

We used a principle which is based on the comparision of responses displayed by the organism to supplied mixtures whose composition varied from experiment to experiment (differentiated) on the one hand, and responses to a mixture which remained unchanged in all the experiments of a given series (undifferentiated), on the other. The character of the undifferentiated mixture depended on the purpose of the experiment being conducted. This was mostly air of ordinary composition (21% O_2 in nitrogen). In any event this was a medium where the component whose effect was being studied had normal composition. For example, if responses to carbon dioxide with various concentrations of oxygen were being studied, then we would use an undifferentiated mixture with a normal, increased or decreased (but constant in experiments of each series) content of oxygen, without an admixture of carbon dioxide. As differentiated mixtures we used those with the same content of oxygen, but with varying concentrations of carbon dioxide. A similar research system facilitated evaluation and interpretation of the data received.

In the experiments with animals in the gas gradient instrument, the gradient of gas composition was set so that an undifferentiated medium was supplied in one end of the chamber, and a differentiated one in the other. In human experiments, two respiratory mixtures were offered: differentiated and undifferentiated. The purpose of the experiment was first of all to explain the tendency of responses to a given differentiated medium: positive if the experimental object preferred that medium in comparison with the undifferentiated one, or negative, if that mixture was rejected and the undifferentiated one was

preferred. There were also cases when no preference was shown and it had to be concluded that the subject organism did not distinguish the offered mixtures.

The distinctive feature of the human experiments lay not only in the fact that active choice occurs specifically by human ability -- by manually switching respiratory mixtures. It is also important that, besides the actually demonstrated preference of one of the offered mixtures, we also considered a particularly human form of response -- the verbal report. At the end of each experiment the subject had to answer the following standard questions: 1) did the offered respiratory mixtures differ from each other; 2) which mixture seemed better; 3) what sensations accompanied the respiration of each mixture. The verbal report was an indication of man's ability to knowingly distinguish between respiratory media and makes it possible to determine more accurately why one or another response was made to an offered gas mixture.

In the overwhelming majority of experiments, the preference expressed verbally for one or other gas mixture concurred with actual choice. If the subject avoided breathing the differentiated mixture, then in his verbal report he indicated that this mixture seemed worse to him, and he noted the unpleasant sensations which it caused. On rare occasions there was a discrepancy between actual choice and the verbal resonses of the subject. For example, a man could not in the time allotted for him choose a mixture, but in his report he indicated a preference which he was inclined to give one of them. If, on the other hand, he avoided one of the mixtures, and in the verbal indication reported them to be equal, perhaps it could be assumed that a choice had occurred subconsciously, and the sensations of the subject in breathing the mixtures did not reach the verbalization level.

For quantitative evaluation of gas preference, we used an index of the choice of the differentiated mixture (S_t) -- the difference between fragments of time during which the experimental object breathed mixtures (differentiated and undifferentiated) relative to the general length of the period of free choice:

$$S_t = \frac{t_d - t_i}{T},$$

where t_d and t_i are the time of respiration (in minutes) of differentiated and undifferentiated mixtures respectively (in animals — total time in corresponding zones of the gas gradient instrument; in man — the period of time over which he breathed each of the mixtures); T is the period of choice (in animal experiments it agrees with the length of complete exposure to the gas gradient instrument).

If, for example, the index of choice by an experimental animal for a determined differentiated mexture is 0.24, this indicated that it avoided a given mixture, and the period of time in the differentiated zone of the gas gradient instrument was 24% less than in the undifferentiated one. In man, such a choice index would mean that the subject breathed in an undifferentiated mixture 24% longer than a differentiated mixture.

* * * *

The present book studies the gas preference response to the following changes in the composition of the respiratory medium:

(1) reduction in oxygen content (hypoxic mixtures);

(2) increase in oxygen content (hyperoxic mixtures);

(3) increase in carbon dioxide content (hypercapnic mixtures);

(4) replacement of neutral nitrogen gas by helium (helio-oxygen mixtures);

(5) different combinations of these factors.

The results of this research, which we performed on rodents and on humans (together with Ye. N. Salatsinskaya and A. M. Shmeleva) are presented in the following chapters.

Chapter II

RESPONSES OF THE ORGANISM TO RESPIRATORY MEDIA WITH
ALTERED OXYGEN AND CARBON DIOXIDE CONTENT

Before discussing gas preference reactions to hypoxic, hyperoxic, or hy-
percapnic media, each time we are obliged to recall briefly several character-
istics of the effect these media have on the basic physiological functions of
higher animals and man and to answer the following questions:

(1)   What are the most important adaptive responses to altered oxygen
      and carbon dioxide contents in the atmosphere exhibited by the
      respiratory system and the systems connected with it; what are
      the thresholds of these responses?

(2)   How effectively are these compensatory shifts able to support an
      adequate gas regime for the organism and its normal vital activity,
      especially the functions of the central nervous system?

HYPOXIC MEDIUM

The most significant respirator response to a medium with lowered partial
pressure of oxygen is an increase of pulmonary ventilation.   The threshold of
ventilator response in man is considered to be a reduction of the oxygen con-
tent of inhaled air to 18-16% (Ellis, 1919; Haldane and Priestley, 1935;
Voytkevich, 1952).   At an ascending altitude, an increase in the volume per
minute of respiration (VRM) can be noticed even on reaching 1000-1200 meters
above sea level (Lutz and Schneider, 1919; Armstrong, 1952).   Apparently ven-
tilation begins to increase when the alveolar oxygen pressure falls to 93 mm Hg
(Hornbein, et al., 1961).   Inhaling a mixture containing 13% O_2 causes

ventilation to increase in only eight seconds (Girard et al., 1959). In the respiration of hypoxic mixtures, the ventilation level is stabilized in one to two minutes, although oxygen saturation of the blood can continue to drop (Dembeau et al., 1965).

Ventilator response intensity depends on the degree of decrease of partial pressure of oxygen (P_{O_2}) in the inhaled mixture. Maximum response (almost double increase of VRM) is observed under the influence of a mixture containing 6 – 8% O_2, or in an "ascent" in a pressure chamber to 7 km (Gray, 1950; Beregovkin et al., 1963).

On the other hand, with an even sharper decrease of the oxygen content of a medium, VRM decreases. In man, such lowering of pulmonary ventilation is observed in breathing a mixture containing less than 6% O_2 (Knowles, 1959) — more precisely, when arterial P_{O_2} drops to 25 mm Hg (Purves, 1966).

Haldane and Priestley (1935) considered frequent and shallow respiration as typical for hypoxia. Actually, according to data from many researchers, ventilator response to an insufficiency of oxygen occurs because of increased frequency of respiratory movements (Seredenko, 1963; Kirchoff, 1963, and others), although several did not observe such an effect in man (Beregovkin et al., 1963; Buteyko et al., 1966). Nevertheless, nearly all the authors agree that respiratory volume (depth of respiration) is certainly increased under hypoxic conditions (Dripps and Comroe, 1947; Asmussen and Nielsen, 1958; Beregovkin et al., 1963; and many others) according to intensification of pulse activity of the respirator neurons in the respiratory center and the muscle-respirator (Kulik, 1967). This leads to a considerable increase of alveolar ventilation, i.e., an increase of that part of inhaled air which directly penetrates the alveoli and participates in pulmonary gaseous exchange. An increase of alveolar ventilation also seems to be the most immediate compensation mechanism for an insufficient oxygen content in an inhaled gas mixture.

An increase in the oxygen supply from lung tissue is another important adaptation to an oxygen deficiency in a medium. This is mostly achieved

because of changes in hemodynamics.

According to Hàldane and Priestley (1937), in man the pulse increases when a mixture containing only 17% O_2 is inhaled. V.I. Voytkevich (1952) noted this reaction under the influence of an 18% mixture (before it is possible to see an actual increase of ventilation), and N.A. Rossolovskiy (1958) noted it in climbing mountains to an altitude of more than 2000 meters. Inhalation of a mixture containing 8% O_2, or an "ascent" in a pressure chamber to 7 km is accompanied by increased frequency of heart contractions to 100 or more beats per minute (Chernyakov, 1960; Richardson et al., 1966).

At threatening degrees of oxygen starvation, tachycardia alternates with pronounced bradycardia. This phenomenon, as well as a decrease of ventilation, is already an indication of the failure of regulatory mechanisms (Armstrong, 1952). In rabbits such response begins with a decrease of arterial P_{O_2} to 30 mm Hg (Horner, 1965). /25

Combined with increased systolic volume (Bershteyn, 1966), increased frequency of heart contractions with a moderate degree of hypoxia leads to a greater volume of blood per minute (Vogel and Harris, 1967), the magnitude of which in man, inhaling a mixture with 8% O_2, can reach 176% in comparison with the initial volume (Richardson et al., 1966). In connection with an increase of vascular tone (Greenfield and Ebert, 1963; Fowler and Read, 1963) the linear rate of the bloodstream also increases (Chernyakov, 1960). Maintaining an adequate oxygen supply to the tissues is also achieved by regulation of the regional vascular tone (Gurevich and Bershteyn, 1966).

Several changes of metabolism must also be attributed to adapting mechanisms. It has been noted for a long time (Kartashevskiy, 1906) that oxygen consumption in animals decreases if the content of that gas in the medium falls below 9%. This phenomenon was subsequently verified in cats (Gubler, 1958) and rabbits (Lyszczarz and Glogowska, 1966).

Our experiments on white mice (Breslav, 1966) showed that upon exposure

to a hypoxic atmosphere, the gaseous exchange of experimental animals decreased. Such a decrease began when the oxygen content in the medium was 15.5% or less. In the interval between 15.5 and 7.5%, the oxygen consumption of the mice correlated almost completely with its concentration in the atmosphere of the gas-exchange chamber. A number of authors have also observed a reduction of gaseous exchange in man at certain degrees of hypoxia. This occurs as a result of inhaling mixtures containing 11-8% O_2 or "ascending" in a pressure chamber to 5-7 km (Sergeyev, 1926; Shick, 1949; Beregovkin et al., 1963). It is true that A.Z. Kolchinskaya (1936) noted an increase of oxygen consumption in people in the pressure chamber at an altitude of 4-7 km, and a decrease only at higher altitudes. The increase in gaseous exchange noted in man during the beginning period of exposure to an hypoxic medium (Alexander and Yegorov, 1947, et al), is probably connected with activation of the described compensatory responses of respiration and blood circulation. The nature of hypoxic decrease of gaseous exchange is not completely clear, but evidently it has a connection with chemical thermal regulation mechanisms under these conditions (K.P. Ivanov, 1959; 1966; Konstantinov et al., 1968).

We will not discuss physiological mechanisms of adaptation to prolonged existence in an oxygen-depleted atmosphere, (that is the topic of Chapter VI), but we will limit ourselves to the question of the effectiveness of the immediate adaptation responses with which the organism responds to hypoxia, and we will attempt to explain to what degree these mechanisms can compensate for the lack of oxygen in a respiratory medium.

Respiration of a mixture composed of 13% O_2 in nitrogen is accompanied by a decrease of alveolar P_{O_2} of almost half — from 100-102 to 50-55 mm Hg (Haldane and Priestley, 1935; Girard et al., 1959). Due to the constancy of P_{CO_2} (38 mm Hg) and water vapor (47 mm Hg), during an altitude increase, the oxygen content falls more quickly in the alveoli than in the surrounding atmosphere. At an altitude of 15 km it reaches zero.

But the most important criterion of compensation for an oxygen deficiency in an inhaled gas mixture is the P_{O_2} of arterial blood. P_{O_2} in blood drops

more slowly than in the alveoli: in hypoxia the alveolar-arterial gradient of P_{O_2} decreases (Schuurmans and Kreuzer, 1967). Besides, the S-shaped oxyhemo-globin dissociation curve enables the blood to maintain a normal oxygen content during small degrees of decreased pressure in alveolar air, and, consequently, in the blood itself. Evidently, a decrease in oxygenation of the blood can be noted in man during respiration of a mixture containing 17% O_2 (Haldane and Priestley, 1935). V. I. Voytkevich (1952) did not detect a decrease of oxygen saturation of the blood in the greater part of experiments conducted inhaling a mixture of 18% O_2; under the influence of a 16%-mixture, such a decrease was noted in several people — 14%,in the majority and 13%,in all subjects. The greater the ventilator response to the hypoxic mixture, the less the oxygenation of the blood decreased.

According to A.Z. Kolchinskaya (1963), during "ascents" of people in a pressure chamber, the following quantities of oxygen saturation are observed in arterial blood:

Altitude (in km)	Oxygen saturation of the blood (in %)
1-3	94 - 89
4-5	88 - 70
5.5-7	70 - 40
8-10	below 40

These data concur with the values obtained by other authors (Vogel and Harris, 1967).

Approximately corresponding degrees of hypoxemia are also revealed in pressure chamber ascents of rats (Tribukait, 1963a).

Of decisive importance in estimating the degree of compensation for an oxygen deficiency in an organism is the pressure of that gas in the tissues, especially in the brain, as it is most demanding of oxygen regime conditions.

Only in recent years has it been possible to explain this by applying polaro-
graphic research methods.

It has been shown with dogs that, in respiration of mixtures containing
10% O_2, the P_{O_2} of the brain comprises 75% of the initial content, and in res-
piration of a 5%-mixture — only 47% (Kovalenko, 1963). In rats, hypoxic media
cause sharper shifts in the oxygen regime of the brain; with only 13% O_2, tissue
oxygen pressure drops in the cerebral hemispheres to 35-45%, and with 9% O_2 to
55-60% (Bernsteyn, 1968). But the insignificant decrease of arterial P_{O_2} still
does not influence the oxygen pressure in brain tissue. This is explained by
the fact that normally the brain works with an excess of partial pressure of
oxygen, comprising approximately 9 mm Hg (Diemer, 1965: Bernsteyn, 1966). And
because of the intensification of the blood supply to the cerebrum (Kety, 1948;
Gurevich and Bernstein, 1966), this organ generally appears to be in a privi-
leged state under hypoxic conditions.

At the same time, the brain's extraordinarily high sensitivity to hypoxia
(Petrov, 1949) allows an inadequacy in the delivery of oxygen to the tissues
to be determined first of all by a disturbance of the functions of the central
nervous system. In "ascending" to an altitude of 1.5 km, rats develop a de-
crease, and, at higher altitudes (8 km), a sharp increase in the threshold of
local irritation in the motor zone of the cortex (Dolina, 1965). In rats,
response to "thermal pain" (intense heating of the tail) (Bullard and Snyder,
1961) decreases during respiration of a mixture with 7.5% O_2, and completely
disappears under the influence of a 5%-mixture. Dogs in the pressure chamber
at an "altitude" of 1-2 km display an intensification of the excitation pro-
cesses and an impairment of differentiations. At an "altitude" of 3-5 km they
show phase conditions, and finally in an "ascent" to 6-7 kms — diffused inhib-
tion and disappearance of conditioned reflexes (Lifshits, 1949). This hypox-
emia causes a breakdown of the dynamic stereotype in dogs, long depression of
conditioned and even unconditioned reflexes (Zvorykin, 1953).

Generally analogous changes in higher nervous activity are noted in man

under hypoxic conditions. Characteristic phenomena during "ascents" in a pressure chamber are: at altitude of 1-3 km — excited mood; 4-5 km — impairment of mental responses, reduction of self-critical ability, and a decrease of efficiency; 5.5-7 km — loss of efficiency; 8-9 km — loss of consciousness (Kolchinskaya, 1963; Ioseliani, 1967). Man's higher nervous activity also suffers when mixtures are inhaled in which the oxygen concentration is lower than 13% (Bernshteyn, 1968). Inhalation of mixtures containing 7% O_2 or less causes a signficant change in handwriting, and deteriorating performance on pyschological tests (Balakhovskiy, 1952).

Characteristic changes are observed in electroencephalograms of man with the inhalation of mixtures containing 12-10% O_2 (or less) and when "ascending" in a pressure chamber to an altitude of more than 4 km (Berger, 1934; Altukhov and Malkin, 1952; Kolchinskaya, 1963; Caspers and Schutz, 1963; Repin, 1965; Madarasz et al., 1965).

Summarizing what has been discussed, it can be concluded that a decrease
in the oxygen content of inhaled air to 18-17% or correspondingly, exposure to an altitude of 1-2 km above sea level, is the threshold of respiratory and circulatory responses to hypoxia.

These responses reach a maximum under the influence of respiration of mixtures with 8-6% O_2 or ascension to an altitude about 7 km.

Strictly speaking, there is no complete compensation for hypoxic shifts when there is an oxygen insufficiency in the respiratory medium (for reasons which will be elucidated in Chapter V). However, because of adaptive responses, shifts of P_{O_2} in the blood and tissues (especially in the brain) occur much more slowly than the oxygen content drop in the inhaled mixture.

A marked impairment of an organism's oxygen regime develops during inhalation of mixtures with 17-16% O_2, or at an altitude of 1.5-2 km. From this moment the first indications of hypoxia of the brain become pronounced. Inhalation of mixtures containing less than 7-6% O_2, or an ascent to an altitude of 7 km

and more, leads to sharp impairment of the central nervous system functions, depression of adaptive responses, and consequently to the organism's loss of ability to compensate in any degree for a shortage of oxygen in the medium.

Let us discuss more throroughly the question of how much the organism is able to discern these degrees of oxygen insufficiency in the atmosphere and how this ability is revealed in the gas preference of animals and man.

Hypoxic Gas Preference in Animals

"And here is what happend at the airfield where they were testing airplanes", says a popular science journal. "Having received the assignment, the test pilot took his place at the controls ... The engines roared, the steel machine rose into the air and began to gain altitude. Already there was nothing to breathe in the airplane compartment. The pilot switched on the oxygen. And here he suddenly noticed a little mouse which had gotten into the airplane — goodness knows how — while it was on the ground. Now the little mouse gasped for breath. And here some sort of unaccountable sense caused him to spring up onto the chest of his terrible enemy — man, and cling to the valve from which a little oxygen was escaping. The little mouse sat in this position until the end of the flight. As soon as the plane descended, the little rodent ran away in a flash."[1]

This incident (if true) indicates that an animal, under conditions of a spatial oxygen gradient, exhibits a negative behavioral response to an hypoxic medium. However, in scientific literature we find no experimental facts of a similar kind. And what is more, Sommers (1963) showed that a tortoise does not distinguish anoxic composition of the air supply in its air bladder when it is immersed into water. But the subject selected by Sommers is not very apt: the low level of gaseous exchange combined with the high oxygen capacity of the blood and the insensitivity of the central nervous system to extreme degrees

[1] See story of B. Rzhevskiy "Trouble Teaches", Nauka i religiya (Science and Religion,) No. 7, 1967, p. 53.

of hypoxia enables many tortoises to breathe under water for a long time (Belkin, 1968).

In our experiments (Breslav, 1963, 1965b), the animals were studied with a gas gradient instrument. A more or less hypoxic medium was created in the differentiated zone (Figure 5)[2].

We found that white mice scarcely react to a mixture where the oxygen content is lowered to 18 and even 15%. But the mice clearly avoided a mixture of 12.5% O_2, preferring, in the overwhelming majority of cases, the undifferentiated (air) zone of the instrument. Negative response was maximum when the oxygen content was 5% at the differentiated end of the chamber. In a medium composed of almost pure nitrogen (2% O_2), the behavior response of the animals was /30 weaker, obviously because of their slowed down state in such an atmosphere. Some of the experimental mice (about 10%) did not even succeed in withdrawing from the hypoxic zone, and died there from acute oxygen starvation.

In white rats the threshold of negative response to hypoxic mixtures was higher and corresponded to 11-10.5% oxygen content in the differentiated zone of the gas gradient instrument. Such a difference could be caused by less sensitivity of rats to an oxygen insufficiency. Figure 6 shows a kymogram which reflects the behavior of a rat in a hypoxic gradient (from 21 to 10% O_2). With a decrease of the oxygen concentration in the differentiated mixtures to 7%, avoidance by the rats of the hypoxic zone increased.

Thus, animals exhibit negative behavior response to a medium with a certain degree of decreased partial pressure of oxygen.

Precisely what factors cause such response? Corresponding research in man must help to answer this question.

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[2] In this and other figures the vertical lines represent standard errors (m).

S_t
+0.3
+0.2
+0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5
-0.6
-0.7
-0.8
-0.9

19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1

☐ 1   ▨ 2

Figure 5. Hypoxic gas preference of rats (1) and mice (2). Average data from 20-40 animals.
Vertically - choice index for the differentiated zone (S_t);

Horizontally - percent of oxygen in the differentiated zone.

10% O_2

21% O_2

0 1 2 3 4 5 6 7 8 9 10
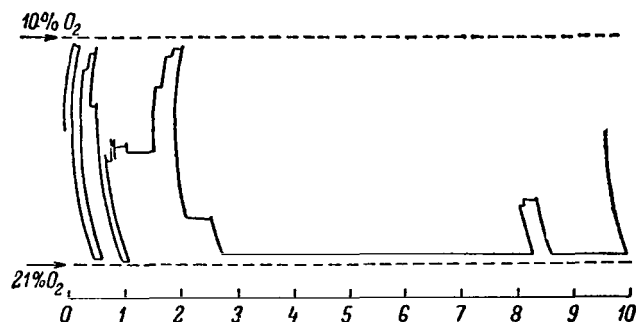
Figure 6. A kymogram showing movement of rats in a hypoxic gradient (from 21 to 10% O_2). There is a distinct preference by the animals for the air medium in comparison with the hypoxic. Beneath - time (in minutes).

Hypoxic Gas Preference in Man

Analyzing evidence from the first balloonists, and also their own experimental observations, Haldane and Priestley repeatedly emphasized the lack of specific sensations which would allow people to notice a vitally dangerous decrease in the oxygen content of the surrounding medium. During a balloon flight (1875) this fact /31 kept Croce-Spinelli, Sivel, and Tissandier from using the oxygen they took with them, and as a result two of them died. Similar observations are also cited by A.A. Sergeyev in his "Ocherki po istorii aviatsionnoy meditsiny" (Essays on the History of Aviation Medicine) (1962).

"Few diseases", writes Armstrong, "are able to cause such extreme changes in an organism (including death) and have at the same time such weak subjective manifestations as altitude sickness. It can often be observed that a man with altitude sickness loses consciousness without any preliminary effects". (1954, p. 221).
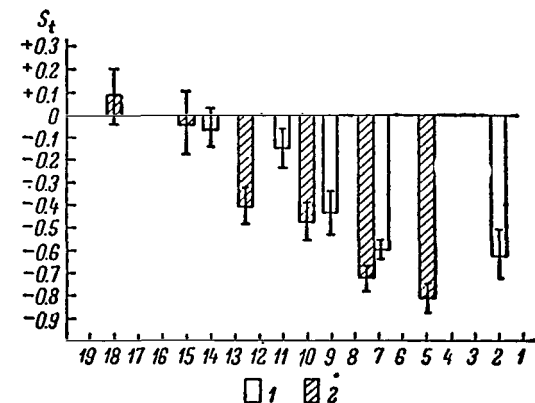
What is more, oxygen starvation is often accompanied by an euphoric

intoxication-like state, concluded by a sudden loss of consciousness. Rapid decrease of the oxygen content in inhaled air also leads to loss of consciousness, sometimes with the sensation of a blow. It is true that in certain degrees of hypoxia (rapid ascent to an altitude of 3-3.6 km or higher) man can feel "general physical lethargy and vague mental anxiety", flickering in the eyes, asphyxia, giddiness, etc. But with further intensification of oxygen starvation, the acuteness of sensations is rapidly dulled, probably because of impaired sensory functions of the nervous system (Armstrong, 1952).

Therefore, in aviation medicine, the use of oxygen for respiration in high-altitude flights (naturally in an unsealed cabin) is absolutely compulsory, regardless of how the crew feels.

The opinion that man is unable to evaluate the adequacy of the oxygen content in a respiratory medium by his own sensations is confirmed by numerous studies of oxygen starvation in an organism (Petrov, 1949, and many others).

At the same time, it cannot be assumed that hypoxic signals do not reach the higher sections of the nervous sytem. In animals as well as in man, conditioned reflexes are quite easily developed, where a respiratory medium with a decreased oxygen content serves as an unconditioned irritant (Voytkevich, 1952; Arkhangel'skaya and Segal', 1954, et al.).

In our research, (Breslav and Salatsinskaya, 1968) during the experiment a man alternately inhaled air (undifferentiated mixture) and a differentiated mixture with a decreased concentration of oxygen (from 18-7%) in nitrogen. In Figure 7 we see the responses of subjects in experiments where the assigned respiration period of these mixtures was limited to five minutes.

Under these conditions it was found that most people did not distinguish mixtures containing 18-15% O_2 from air; some subjects avoided a 12% mixture. Media with 10.5-9% oxygen concentration caused statistically significant negative response. Finally, an even more depleted mixture (7% O_2) was rejected in nearly all cases.
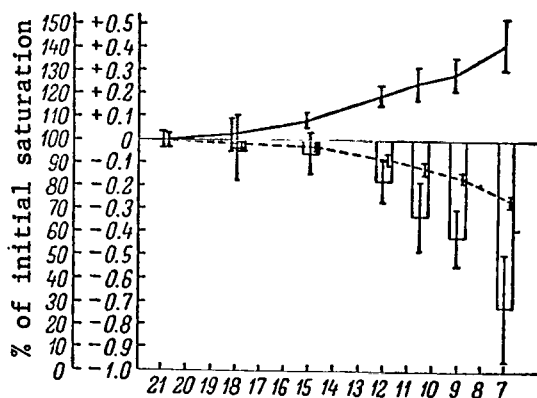
Figure 7. Hypoxic gas preference of man. Average data from 45 subjects. Columns — choice index for the differentiated zone (S_t); Solid line — VRM; Broken line — saturation of the blood with oxygen (in % of the initial). Horizontal — % of oxygen in the differentiated mixture.

In choosing the mixtures, the subjects cited unpleasant sensations which were characterized in verbal reports mostly as "it is difficult to breathe"; more rarely as "suffocating", "not enough air", "dizziness", "cloudy vision", etc. Such sensations as a rule did not appear before the 2nd–3rd minute of breathing an hypoxic mixture. One of the experiments is shown in Figure 8, where the differentiated mixture contained 9% O_2.

If we compare, on the one hand, the curves of increased pulmonary ventilation and decreased oxygenation of the blood with, on the other, the responses of the subjects to these mixtures (gas preference), it can be noted that the degree of avoidance of one or other mixture is generally proportional to the hypoxemia caused by it. Actually, the negative choice of hypoxic mixtures by the subjects correlates very well with the percentage of incomplete oxygen saturation of the blood, and less well with the intensity of ventilator response to these mixtures. Corresponding correlation coefficients are + 0.99 ± 0.05 and −0.92 ± 0.13.

This revealed that the time during which the hypoxic medium acts also has an influence.

Let us consider subject response to 5-, 10-, and 15-minute inhalations of slightly (15%), moderately (12%), and significantly (9%) depleted oxygen gas mixtures (Figure 9). During respiration of hypoxic mixtures, pulmonary ventilation /34 reached a maximum in the 1st-2nd five-minute period. By the fifth minute, alveolar air has an almost constant composition. Oxygenation of the blood continued to
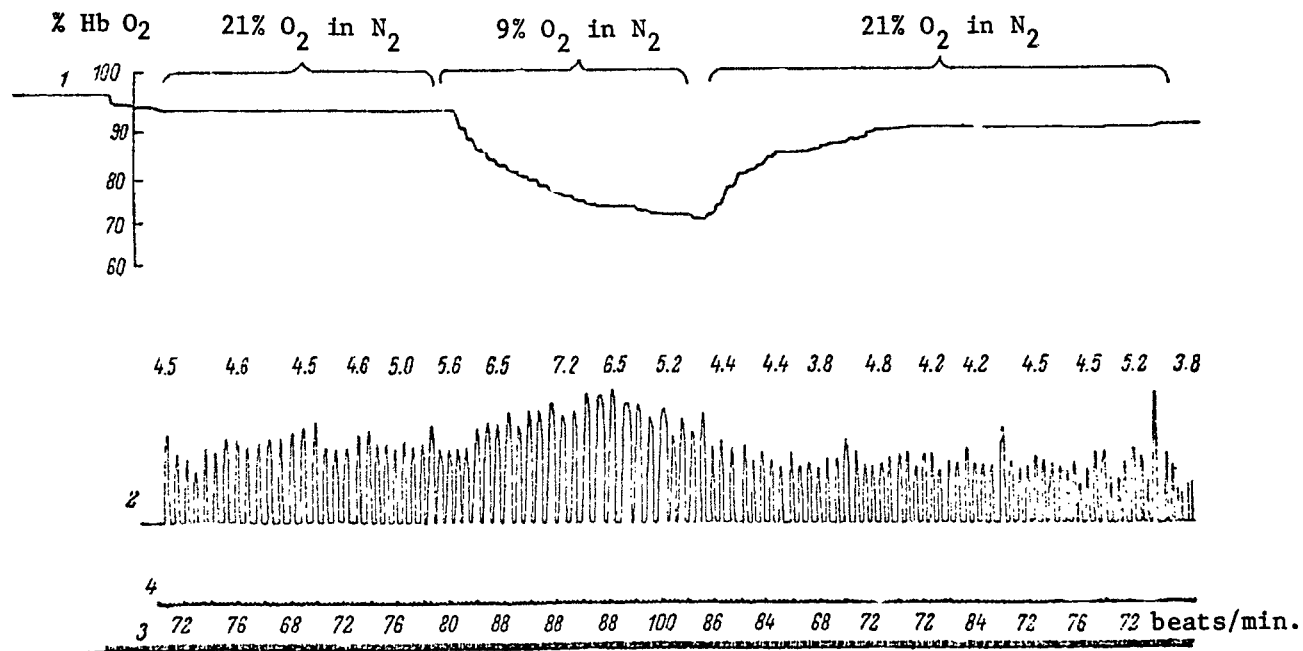
Figure 8. Saturation of the blood with oxygen (1), spirogram (2), and pulse (3) of a man breathing air and a hypoxic mixture. Preference by the subject for the air mixture in comparison with the hypoxic is distinct. Figures: in 2 -- VRM (in liters); in 3 - pulse (in beats/min); 4 - time, 5/30 sec.
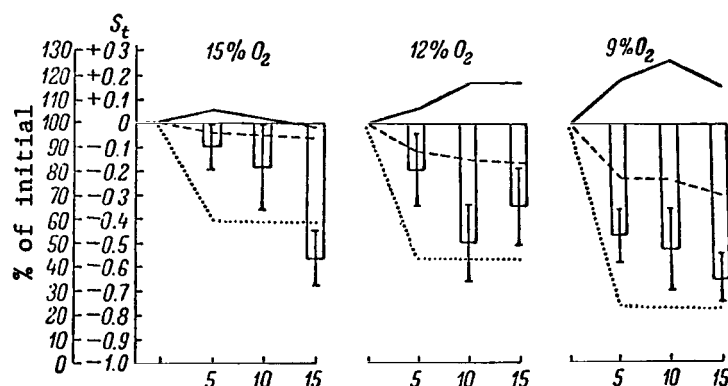
Figure 9. Responses of man to hypoxic mixtures in various lengths of breathing time. Average data from 12 subjects. Dotted curve - alveolar P_{O_2}. Horizontally - length of periods breathing given mixtures (in min.). The rest of the legend is the same as in Figure 7.

decrease to the 15th minute, but not nearly as sharply as in the first five minutes. At the same time, negative choice of slightly and moderately hypoxic mixtures developed only if respiration time subsequently reached 10 or 15 minutes. Thus, the more oxygen-depleted the gas mixture and the greater decrease of oxygenation of the blood it causes, the less time man needs to distinguish this mixture from air.

Inhalation time and the degree of hypoxemia necessary for man to distinguish hypoxic mixtures were studied in this form:

Oxygen content in respiratory mixtures (%)	Length of given respiration period in which subjects reliably distinguish mixtures (in min.)	Average decrease of oxygenation of the blood by end of the inhalation period (%).
15	15	9
12	10	17
10.5	5	24

It may be inferred that avoidance of hypoxic media does not develop simply with a certain decreased oxygenation of the blood, but just at that moment when some total oxygen deficiency is established in the organism.

But if this is so, then man must also detect his own hypoxic condition when the oxygen content in a medium decreases gradually and evenly.

As a matter of fact, A.B. Gandel'sman (1965) showed that it is possible for man to develop the ability to evaluate quite accurately, on the basis of natural sensations, the oxygenation level of his own blood when hypoxia was gradually developed during respiration in a closed system.

We conducted a similar experiment to explain a somewhat different problem: at what moment can man, not previously specially trained, give a verbal report about his change of sensation if the oxygen content is decreased gradually, and not suddenly as with switching respiratory mixtures.

The experiment was as follows. The subjects breathed air through a mouth-piece for 5 minutes, then switched to a closed system of return respiration (Krogh apparatus)*. The oxygen content in the air of the system gradually decreased in proportion to oxygen consumption. Liberated carbon dioxide was absorbed by sodium lime. At the moment when the subject noticed "a change in the composition of the respiratory mixture" (a statement in the instructions). he gave a signal. Then return respiration continued until the onset of expressed signs of oxygen starvation (tremor, damage to muscular tone, loss of consciousness) or until the subject indicated a feeling of the impossibility of further respiration. In this last case, he himself switched to air respiration. After the experiment, the subject gave a verbal report of his sensations.

As shown in Figure 10, a change in how the subject felt usually began in the 8-9th minute of return respiration in the closed system. The sensations

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*Translator's Note: Named after a Danish physiologist noted for research on the capillaries.
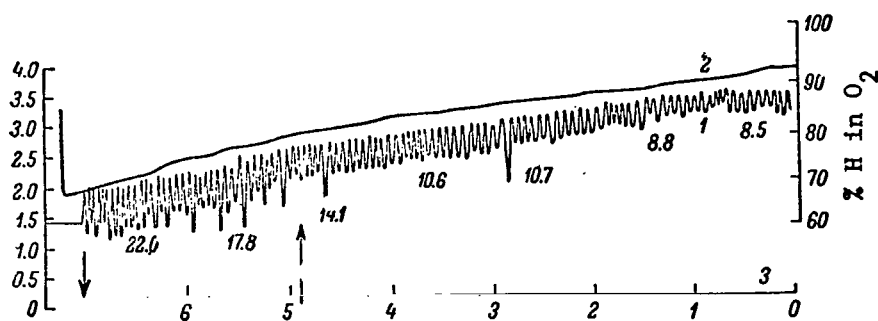
Figure 10. Spirogram (1) and oxygen saturation of the blood
(2) in man in return respiration and gradually increasing
hypoxia.
   Figures – VRM (in liters); upward arrow – the moment when
   the composition of the inhaled mixture is distinguished;
   downward arrow – active switching to air; 3 – time (in
   min); left – scale of respiratory volumes (in liters);
   read from right to left.

noted mostly were labored breathing, shortage of air —— more rarely, giddiness
and a pounding in the temples. At this moment the average oxygen content in
the medium was about 10%, and oxygenation of the blood was about 80%. After
this the subject could still breathe in the closed system for 2-3 minutes until
the experiment ended. The oxygen content in the system by the end of the ex-
periment fell to 6%, but oxygenation of the blood fell to 60% or somewhat
lower.

In several respects the data resemble parallel observations in man made
by I.S. Balakhovskiy (1952) of the changes in bioelectric activity of the brain
and oxygen saturation of the blood during respiration of an hypoxic medium.
With oxygenation of the blood to 67-78% O_2, an encephalogram showed isolated
slow fluctuations: this conforms to the first indications of impairment of
higher nervous activity (change of handwriting, extended time of psychic
response). With saturation of the blood to 48-68% O_2, groups of shallow fluc-   /36
tuations developed, and shortly after the subject required an end to the
experiment.

Thus, both animals and man distinguish a change in the composition of an
inhaled mixture if its oxygen content decreases about half. This moment

corresponds to a significant decrease in the oxygenation of the blood and increased pulse frequency. Partial pressure of oxygen, corresponding to the threshold found in our experiment, which develops with hypoxic preference, takes place under natural conditions at an altitude of 4-5 km above sea level.

In aviation medicine, this region is called the partial compensation zone: certain disturbances of a number of physiological functions of the organism appear here. If we confine ourselves to the classification suggested by A. Z. Kolchinskaya (1963), this indicates the stage of so-called compensatory hypoxia (which changes to the latent hypoxia observed at an altitude of 1-3 km). At this stage in addition to respiratory responses, mechanisms are activated which increase the blood supply to vitally important organs. In essence, this compensation is not complete. This is expressed by the indicated changes in a number of functions, especially those of the central nervous system.

Maximum negative responses in mice and rats to mixtures containing 5-7% O_2 correspond to the sharp (approximately half) decrease of oxygen saturation of the blood in animals and indications of tissue hypoxia (Atland et al., 1967).

Therefore, negative response to an hypoxic respiratory medium is evidently /37 connected to the development of a non-compensatory disturbance of the oxygen regime in the organism, more accurately, of ɛ certain degree of oxygen deficiency.

HYPEROXIC MEDIUM

Under natural conditions land creatures never encounter increased partial pressure of oxygen in the atmosphere; therefore hypoxia appears to be a non-biotic factor.

Neverthless, respiration of oxygen-enriched mixtures causes uniform responses from a number of the organism's systems. A study of these responses does not have only theoretical importance. Oxygen is widely used as a therapeutic means. Divers must often work in a medium that has increased partial pressure

of oxygen. At least in some cases, cosmonauts will probably also have to breathe hyperoxic mixtures.

The majority of researchers note that in breathing pure oxygen or hyperoxic mixtures (containing more than 30% O_2), pulmonary ventilation in animals and man decreases (Campbell, 1928; Euler and Liljestrand, 1940-41; Zhironkin, 1956; Lembertsen, 1963b; Kovalenko et al., 1964; Mürtz and Begenat, 1965) in accordance with decreased pulse activity of inspirator neurons and muscles (Kulik, 1967). It is true that several authors, on the other hand, consider moderate hyperventilation to be characteristic of hyperoxia (Behnke et al., 1935; Golodov, 1941; Heck and Loschcke, 1942; Cross and Warner, 1951; Brandis et al., 1960).

Detailed observations have shown that even in 2-6 seconds after the beginning of inhalation, oxygen causes decreased ventilation. This lasts 1-3 minutes and, according to various data, comprises 3 to 31% of the original level. Such a decrease of VRM is evidently explained by deactivation of hypoxic stimulation of arterial hemoreceptors, by their "physiological denervation", which is treated in Chapter V. With subsequent respiration, in connection with secondary shifts (acidification of blood because of increased oxyhemoglobin content and other factors), ventilation again reaches the original level or even exceeds it (Dripps and Comroe, 1947; Dejours, 1962; Backsliger et al, 1963).

A reduction in respiratory movement is a more stable response to hyperoxia (Bert, 1878; Briggs, 1920; Binet and Bochet, 1955; Zhironkin, 1956; Zhironkin et al., 1965; Gleason and Edwards, 1963).

Thus, respiratory responses to excessive oxygen content actually lead to significant changes of alveolar ventilation and cannot have serious adaptive importance. /38

The case of the cardio-vascular system is evidently different. A slowing down of the pulse is quite characteristic in hyperoxia (Ananov, 1873; Bert, 1878; Behnke et al., 1935; Berkovich and Shakhnovich, 1940; Meda, 1950;

Sorokin, 1960; Redderson and Grawenstein, 1964; Mollaret et al., 1965). At the same time, the systolic and per minute volume of blood decreases (Anthony, 1940; Sorokin, 1960; Aber et al., 1964). Arterial pressure, according to the majority of authors (Bezugliy, 1958; Backsliger, 1965; et al.) drops.

A result of these shifts is a reduction of the bloodstream rate (Sorokin, 1960; Jackobson et al., 1963; Redderson and Grawenstein, 1964), which in turn reduces the oxygen supply from the lungs to the tissues. Limiting oxygen transport also causes a decrease in the mass of circulating blood (Sorokin, 1960) and constriction of peripheral vessels (Brandgendler, 1927; Sorokin, 1960; Redderson and Grawenstein, 1962; Robert, 1965), in particular those of the brain (Tinel, 1927; Dumke and Schmidt, 1943; Klossovskiy, 1951; Lambertsen et al., 1953; Womack, 1961; Bergofsky and Bertun, 1966).

A discussion of the effects observed in prolonged respiration of hyperoxic mixtures under pressure does not enter into our task. It is well-known that such effects cause a complex group of phenomena of oxygen poisoning in the organism, characterized by qualitatively different shifts of physiological functions.

How does the oxygen regime of an organism change in hypoxia?

Alveolar oxygen pressure in air respiration comprising 102-107 mm Hg increases with inhalation of a mixture of 50% oxygen and nitrogen to 300, and in respiration of pure oxygen to 650 mm Hg (Meda, 1950; Bishop and Cole, 1962). However, inspiration of hyperoxic mixtures impairs the distribution of gas in the lungs (Howard and Penman, 1967). In connection with a change of the ventilator-perfusion coefficient, the alveolar-perfusion gradient P_{O_2} increases, so that oxygen pressure in arterial blood is increased somewhat less in comparison with alveolar blood (Lenfant, 1965, et al.). This is also assisted by the opening of arteriovenous anastomoses (bypasses) in the pulmonary cycle (Bishop and Cole, 1962, and others).

Nevertheless, arterial P_{O_2} increases 5-6 times during respiration of pure

oxygen (Said et al., 1961) reaching 400-500 mm Hg in the first 1-2 minutes (Heller and Watson, 1961). The oxygen content of the blood increases almost exclusively because of dissolved gas by 2.2 - 2.4 vol. % or by 10-12% of its content in the blood during air respiration (Anthony, 1940; Dedyulin, 1949; McDowall, 1964; Mollaret et al., 1965). The point is that oxygenation of hemoglobin in arterial blood, normally constituting 96-97%, reaches 100% with an alveolar P_{O_2} of 170-180 mm Hg (arterial P_{O_2} corresponding to 130-140 mm), i.e., in breathing a mixture containing 35% O_2 (Mattes et al., 1937; Douglas and Edholm, 1949; Kress, 1959; Honda and Kreuzer, 1966).

Because of these facts, oxygen pressure in the tissues, especially in the brain (where, as has been said, the vessels undergo spasms), increases comparatively little (Marshak, 1963; Grechishkin, 1964; Zhironkin et al., 1966; Ackerman and Brincley, 1966; Bergofsky and Bertun, 1966). Within 1 - 1.5 minutes after the beginning of inhalation, respiration of oxygen causes an increase of P_{O_2} (maximum) in various sections of the brain of not more than 1.5 - 2 times, compared with normal (Kovalenko and others, 1961, 1964; Ilin, 1966). Oxygen pressure in the spinal fluid increases slower than in the blood (Backsliger, 1965; Gaudebout et al., 1965).

Hyperoxia is accompanied by several functional shifts in the central nervous system, although incomparably less apparent. In an oxygen-enriched atmosphere (30% and more), certain changes in the electroencephalograms of rats have been recorded (Caspers and Schütz, 1963). Even in short-term respiration of hyperoxic mixtures (from 55 to 100% O_2) regular fluctuations were noted in higher nervous activity (Rickle and Krivoshenko, 1948; Zilov, 1953; Zhironkin, 1956). Changes in psychic functions under the influence of oxygen have also been described in man (Upenskiy, 1870; Lehmann and Graf, 1942, and others).

Therefore, respiration of pure oxygen or hyperoxic mixtures causes in man and animals several shifts in respiration and blood circulation. These develop even in the first minutes of inhalation. Principally because of compensatory hemodynamic responses, and also because of the fact that the oxygen content in

the form of oxyhemoglobin (i.e., basically its carrier in the blood) does not increase much, increased oxygen pressure in the tissues, especially brain tissues, occurs to much lesser degree than in the respiratory medium. Nevertheless, respiration of mixtures containing more than 30-50% O_2 are accompanied by several changes in the functions of the central nervous system.

Let us now discuss data which concern behaviorial responses of animals and man to a hyperoxic medium.

Hyperoxic Gas Preference in Animals

In the experiments of Z.P. Kuznetsov (1958) dogs were repeatedly made to breathe pure oxygen; at the same time their paws were stimulated by an electric current. As a result of these combinations, delivery of oxygen to the respiration mask began to cause active withdrawal of the animals' paws. This seems to indicate that some kind of signal entered the higher sections of the central nervous system. This signal, connected with the hyperoxic condition of the organism, is very weak to be sure (the described conditioned reflex took 75-80 combinations to develop).

Evidently animal behavior in a medium with local increased oxygen content has not yet been studied.

In our experiments, a hyperoxic medium (70-90% O_2) was created in the differentiated zone of the gas gradient instrument. Experiments on rats showed that the reaction to such a mixture was not the same in animals of different age groups. In Chapter VI, where shifts of gas preference in ontogenesis will be the subject of a special discussion, we will support the assumption that there is a connection between these reactions and age characteristics of an organism's oxygen regime.

Hyperoxic Gas Preference in Man

"Is it possible to distinguish air from oxygen in respiration?" — the research of Bartlett and Hertz (1962) was published under this title. Healthy people (pilots) were offered alternately ordinary air and pure oxygen to breathe. Interrogation showed that the subjects could neither confidently distinguish between these media, nor accurately determine "which was which". All the answers had a random distribution. From this fact the authors drew a somewhat unexpected conclusion: as long as a man does not know exactly what he is breathing, then medical application of oxygen ... is useless (if there is no deficiency of this gas in the atmosphere or in the unhealthy respiration organs). By the same rule, we can say that all medicine is useless that does not have a particular taste! Nevertheless, the work of Bartlett and Hertz is of great importance, as it is, evidently, the only published research devoted to man's distinguishing an hyperoxic medium, even though oxygen inhalation for therapeutic purposes has been widely practiced for nearly two hundred years.

Judging from our research (Figure 24), people really distinguish poorly between oxygen and air. But one cannot say that this ability is completely absent in man. A considerable portion of the subjects noticed a difference in /41 sensations upon breathing air, on the one hand, and almost pure oxygen (98%) on the other. It is true these distinctions did not produce any specific verbal statement. In the majority of cases, the subjects indicated that oxygen was "harder to breathe", and avoided breathing this gas, preferring the air mixture. A choice index for a 5-minute period of a given respiration was -0.33 ± 0.15, for a 10-minute period, -0.42 ± 0.16.

During respiration of oxygen, ventilation dropped in the first 1-2 minutes, and then was established higher than originally, which corresponds to the data presented by Dejours, Backsliger, and others. The experiments shown in Figure 11 can serve as an example.

The avoidance of oxygen can be attributed, it seems to us, to a passing response to hyperoxia, mostly to its spasm action in brain vessels. The

21% O$_2$ in N$_2$ 98% O$_2$ 21% O$_2$ in N$_2$

% HbO$_2$ 100

90

7.4   7.2   7.4   7.4   7.6   6.8   7.4   7.5   8.4   8.2   9.2   6.6   6.8   7.4   7.8   6.6   7.6   8.0   6.8   7.8   7.6   8.2   7.4
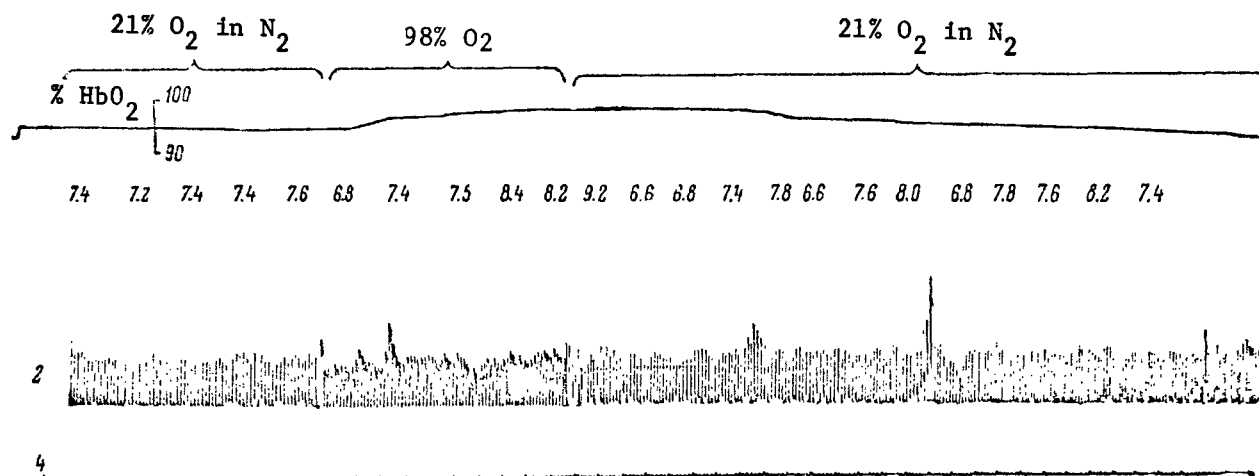
2

4

Figure 11. Man's respiration of air and pure oxygen. The distinct preference of the subject for air in comparison with oxygen is shown. Legend the same as in Figure 8.

following fact can serve as indirect confirmation of that. If carbon dioxide was added to both respiratory mixtures (both the undifferentiated and the differentiated) in equal concentrations (3.5%), then the majority of subjects did not avoid the oxygen, but preferred it (selection index was +0.29 ± 0.13). It is known that if hyperoxia, as has been emphasized, causes constriction of the vessels in the brain, then excess carbon dioxide in the blood lessens this effect and leads to vasodilation (Lambertsen, 1963a, 1963b). It is true that for the same reason positive response to oxygen is developed in people when breathing in an extended artificial stagnant area, which is created by the activation of a crimped tube between the mask and the breather valves. Under these conditions 80% of the subjects preferred to breathe oxygen instead of air.

We will consider response to oxygen with a background of hyperoxymia separately. Against such a background, especially at certain altitudes, a positive attitude is clearly developed in man toward breathing oxygen (see Chapter VI).

It may be inferred that response to a hyperoxic medium in any degree reflects the state of the oxygen regime of an organism at a given moment. A study of these responses under normal conditions and in pathology can be useful in demonstrating response to inhalations of hyperoxic and in some cases to hyperoxic-hypercapnic mixtures. This is not only a question of oxygen therapy for respiratory, circulatory and other disorders which lead to general or local oxygen deficiency (Dembeau, 1957; Sorinson, 1960; Levine et al., 1967; and many others). It also concerns the use of an oxygen-enriched respiratory medium for healthy people when there is sharply increased energy expenditure, mostly in strenuous muscular activity (Marshak, 1961; Anisimov, 1968; and others).

In any case, man's ability (even though it is weakly expressed) to distinguish oxygen from air indicates that physiological shifts occurring with /43 even the brief influence of a hyperoxic medium have an influence on the organism.

HYPERCAPNIC MEDIUM

Although carbon dioxide is one of the least significant components of the atmosphere, as the end product of biological oxidation it plays a special role in the respiratory function of an organism.

N.M. Al'bitskiy (1918) stressed that an organism supports internally a certain carbon dioxide content, preventing both its excess (hypercapnia) and its deficiency (hypocapnia).

We will discuss here the responses observed in man and in animals in inhaling mixtures with moderately increased carbon dioxide content.

Respiration of hypercapnic gas mixtures causes, as a rule, a ventilator response, aimed at flushing out the excess carbon dioxide from the organism. Under the influence of carbon dioxide, the volume of respiration per minute increases in man (Miescher-Rusch, 1885, cited by: Haldane and Priestley, 1935; Haldane and Priestley, 1935*; Conradi and Bebshina, 1936; Sechzer et al., 1960; Fuleihan, et al., 1962; and many others), as well as in animals (Haldane and Smith 1893, cited by: Haldane and Priestley, 1935; Backsliger, 1960; and many others).

Judging from published data, the minimum concentration of carbon dioxide needed to produce ventilator response is 0.4 - 0.7% (Golodov, 1941; Pogrebkova, 1965; Yu.N. Ivanov, 1966). Generally the respirator is so sensitive to this factor that it is very difficult to determine here a threshold reaction (Otey and Otis, 1962); the result evidently depends on the accuracy of the method used.

Ventilation gradually increases with increased concentration of carbon dioxide. Therefore, a 2% concentration of CO_2 causes VRM to increase 20-40%; a 3% concentration causes it to increase 2 - 2.5 times. Maximum ventilator response (an increase of almost 10 times) is observed with a 10% concentration of CO_2 (Knowles, 1959, and others).

*Translator's note: Cited twice in the original text.

VRM increases especially sharply if carbon dioxide pressure increases in alveolar air. Haldane and Priestley showed that ventilation doubled when the alvelolar content of CO_2 was increased by 0.23%. The VRM increase is related to alveolar P_{CO_2} of a certain linear dependence (Lloyd et al., 1958; Otey and Otis, 1962; Dejours et al., 1965). This makes it possible to use an equation (Lloyd et al., 1958) and even to build a model (Grodins et al., 1954) for /44 predicting respiration responses to hypercapnia. For each 1 mm Hg that alveolar P_{CO_2} increases, VRM normally increases by 2.27 liters (Lambertsen et al., 1963). This value is usually called the slope curve of ventilator response to hypercapnia. The beginning of the curve corresponds to alveolar P_{CO_2} of 27-28 mm Hg (Hanks et al., 1961). Thus in ordinary respiration of air (alveolar P_{CO_2} about 38 mm), ventilation is essentially already under the influence of hypercapnic stimulation.

Inhalation of one — two respiratory volumes of a mixture with 6% CO_2 causes ventilator response in only 5-10 seconds in both man and dogs, reaching a maximum in 5 seconds (Bourverot et al., 1961, 1963). After the beginning of respiration of a hypercapnic mixture, as well as after switching back again to air respiration, ventilation changes slower than the arterial pH and P_{CO_2}, but more slowly than the indices of the spinal fluid (Lambertsen et al., 1961). But despite the regularity of ventilator response, in repeated experiments it is unreproducible in an accurate quantitative expression because of attendant respiration deviations (Read et al., 1964). Although moderate tachypnea can accompany ventilator response to carbon dioxide (Salzano and Hall, 1960, et al), VRM increases basically because of an increase in the depth of breathing (Haldane and Priestley, 1935; Berkovich, 1939; Zheludkova et al., 1964). This guarantees an effective increase of alveolar ventilation (Comroe et al., 1956).

According to some data, carbon dioxide causes an increase in the vital capacity of the lungs because of expansion of the bronchi (Whittenberger, 1962; Samanek and Aviado, 1967). It is true, however, that other authors (Nadel and Widdicombe, 1963) observed in man a constriction of the bronchi in respiration

of mixtures with 2 - 8% CO_2. Finally we must point out the increased diffusion ability of the lungs discovered under the influence of a hypercapnic medium (Rankin et al., 1960; Hyde, et al., 1964).

Therefore, within certain limits increasing carbon dioxide in inhaled air causes totally suitable respiratory responses, aimed at increasing the efficiency of alveolar ventilation and preventing carbon dioxide retention in the organism.

Increased removal of carbon dioxide is also ensured by reactions in blood circulation. A number of authors note that hypercapnia slows down the rhythm of heart contractions (Salzano and Hall, 1960; Greenfield and Ebert, 1963; Mithoefer and Kazemi, 1964; Zheludkova and others, 1964). It is true that several observed tachycardia in man in respiration of carbon dioxide-rich mixtures (Sechzer et al., 1960; Albano and Indovina, 1962). In hypercapnia, systolic volume increases (Linde et al., 1961). The volume of blood per minute is also amplified (Dembeau 1957; Nakada et al., 1965). Arterial pressure also increases (Sechzer et al., 1960; Cross and Silver, 1963; Manley et al., 1964). /45

At the same time the vessels begin to dilate as a result of the local activity of carbon dioxide in them (Brandgendler, 1927, et al). It is especially important to note the dilating activity of hypercapnia in the vessels of the brain (Dumke and Schmidt, 1943; Marshak et al., 1948; Lambertsen et al., 1953; Sanotskaya, 1962), leading to an increase of the brain's blood stream (Hegedus and Shackelford, 1965).

We must discuss further the question of how much these adaptive responses of the respiratory and cardio-vascular system provide compensation for beginning shifts in specific sections of an organism's gas regime under exogenous hypercapnic conditions.

Haldane and Priestley, and I.M. Sechenov before them, noted the exceptional uniformity of the alveolar pressure of carbon dioxide: in respiration of mixtures with 2 - 3% content of carbon dioxide it increased very insignificantly.

The more sensitive is the ventilator response to carbon dioxide, the less it increases (Dejours et al., 1965). While the concentration of carbon dioxide in the inhaled air is much lower than in alveolar air, ventilator response compensates the hypercapnia to a considerable degree, and alveolar P_{CO_2} can sometimes even decrease to less than normal (its own form of overregulation). Only after long exposure to a hypercapnic medium, when gradual reduction of VRM begins, is this compensation impaired. This can cause an increase in both alveolar and arterial pressure of carbon dioxide (Zharov et al., 1963; Zagryadskiy and Sulimo-Samuyllo, 1963). But if the concentration of carbon dioxide in the medium begins to approximate the alveolar concentration (more than 3%), compensation is inhibited and alveolar P_{CO_2} increases (Yamamoto, 1957). An especially sharp jump of this characteristic is observed when the carbon dioxide content in an inhaled mixture reaches 6%, i.e., exceeds the alveolar content (Krogh, 1959). The alveolar-arterial gradient of carbon dioxide, naturally, is distorted, but arterial P_{CO_2} increases sharply (Pierce et al., 1962; Ypersele et al., 1962; Matell, 1963; Hostetler and Manning, 1964).

The tissue pressure of carbon dioxide is increased in approximately the same circumstances as alveolar and arterial pressure in respiration of hypercapnic mixtures. An increase of P_{CO_2} in the myocardium, the brain and in other tissues (Sanotskaya, 1962; 1966; Van Liew, 1963; Korol'kov, 1964, et al.) is noted. Carbon dioxide in arterial blood is equalized with cells from the respiratory center in approximately 4 minutes (Anderton and Harris, 1963; Bradley et al., 1963).

We will not dwell here on the biochemical shifts which appear in hypercapnia, in particular the generally known respirator acidosis.

A few words about the influence on the central nervous system of breathing carbon dioxide-enriched mixtures. Hypercapnia is revealed by a depression of motor activity and inhibited responses to internal stimuli in rabbits and mice in a 3-5% concentration of carbon dioxide in the atmosphere (Doronin, 1963; Zheludkova and others, 1964). In a 1 1/2-hour exposure, a CO_2 content of

from 6 to 7% causes the most extreme inhibition (Baranatskiy, 1960). Respiration of a mixture with 10-20% CO_2 produces a sharp decrease of activity on an electroencephalogram (Repin, 1962; Grandpierre et al., 1967).

With a concentration of only 3% CO_2 in a medium, a fairly long exposure causes behavior disturbances in man (Schaefer, 1961). Respiration of a mixture containing 6% CO_2 lowers efficiency (Brestkin et al 1934, cited by Zheludkova et al, 1964), but inhalation of 10% CO_2 leads to a state of deafness, and the experiment must be ended (Haldane and Priestley, 1935). Study of a man's encephalogram shows that respiration of a medium with 5% content of CO_2 causes desynchronization in the EEG of the frontal lobe stem, and 8-10% content causes it in other regions of the brain (Yu. Ivanov, 1961).

In adaptive responses to hypercapnia, the greater or lesser gradual increase of this factor is important. Thus a rapid transition to a mixture containing 5-6% CO_2 is not endured well by man (Aver'yanov et al, 1935; White and Benson, 1952), although if the concentration of carbon dioxide is increased slowly he can breathe such mixtures for several hours (White and Benson, 1952; Tenney, 1963).

Therefore, although an organism develops various adaptive responses to hypercapnia, these responses do not always provide sufficiently complete compensation for the shifts which are caused by breathing mixtures containing an excess of carbon dioxide.

Not long ago it was shown that in breathing carbon dioxide-enriched mixtures (exogenous hypercapnia) as well as in muscular work (endogenous hypercapnia) similar relations were observed between pulmonary ventilation and the pressure of carbon dioxide in combined venous blood. For each 1 mm Hg that venous P_{CO_2} increases, VRM increases 2.8 liters (Riley et al., 1963).

At the same time, the level of ventilation does not have such an immediate relation with arterial P_{CO_2}. It is also understood that regulation of respiration depends on the intensity of the exchange, and, consequently, on the quantity

of carbon dioxide produced in the organism. This is precisely what is reflected by the magnitude of combined venous P_{CO_2}. Thus, respiration is regulated in accordance with the level of endogenously produced carbon dioxide, i.e., with the metabolism level in the tissues.

When partial pressure of carbon dioxide is increased in inhaled air, the same mechanisms are evidently activated as in endogenous hypercapnia. While the concentration of carbon dioxide in the atmosphere is still so small that it can be disregarded, adaptive responses seem perfectly adequate. But when the content of carbon dioxide in the respiratory mixture becomes equal to the alveolar content, the increase of alveolar ventilation progressively lags behind what is necessary, computed on the basis of the equations of I.M. Sechenova (Brestkin, 1952). If the P_{CO_2} in the medium is equal to alveolar P_{CO_2}, no hyperventilation can any longer prevent the growth of alveolar P_{CO_2}. But when the content of carbon dioxide in the inhaled mixture becomes considerably greater than in the alveoli, then increased ventilation (which still continues to intensify within a certain range) progressively increases the hypercapnia. Then — there are disturbances in the function of a number of the organism's systems, including the brain.

In this respect the short-lived effect of a hypercapnic medium can be separated into three gradations according to the content of carbon dioxide in inhaled gas mixtures:

(1) adequate (although not absolutely complete) compensation (to 3% CO_2);

(2) inadequate compensation (3 - 5.5% CO_2);

(3) uncompensated hypercapnia (over 5.5% CO_2).

We will proceed to the question of the distinction of hypercapnic mixtures by man and animals.

Figure 12. Hypercapnic gas preference of rats and mice. Average data from 20 - 30 animals. Horizontally - percent of carbon dioxide in the differentiated zone. The rest of the legend is the same as in Figure 5.
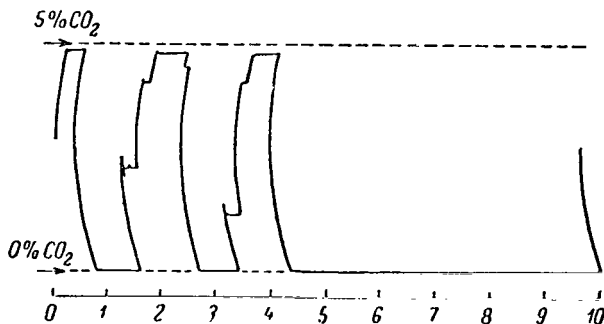
Figure 13. Kymogram of the movement of a rat in a hypercapnic gradient (from 0 to 5% CO_2). Distinct preference of the animal for air in comparison with the hypercapnic medium. Below – time (in min).

Sommers (1963) has studied behavioral responses of animals to hypercapnic media. A rat was placed in a small chamber. A gas mixture containing from 8 to 15% CO_2 was blown through the chamber. When the animal pushed a special plate, the hypercapnic mixture was shut off. In this way a motor act of avoiding the carbon dioxide was developed. Sommers thinks that the threshold of this response lies somewhat below 8% CO_2. The response becomes stronger in proportion to the increased concentration of carbon dioxide in the mixtures offered.

We studied the gas preference of rats and mice to hypercapnic media (Figure 12). A definite response was not observed with small concentrations of carbon dioxide (1%); some of the animals even preferred a weakly hypercapnic medium to the air medium. The experimental animals began to avoid the differentiated zone of the gas gradient instrument when the concentration of carbon dioxide reached 3-4% there.

After several approaches to the hypercapnic end of the chamber, the animal /48 usually chose the air zone (Figure 13). This response appeared with maximum intensity under the influence of 10-12% CO_2.

In this way, the threshold of negative response to an hypercapnic medium in animals corresponds roughly to those concentrations of carbon dioxide which initiate the under-compensated hypercapnic shifts in an organism.

Hypercapnic Gas Preference in Man

As far back as 1936, G.P. Konrady and Z.V. Bebeshina demonstrated conditioned-reflex hyperventilation in man under the influence of undifferentiated stiumuli which had been associated several times with breathing an admixture of carbon dioxide. Conditioned changes of respiration could also be noted when people were subjected to hypercapnia — acute (inhalation of mixtures with carbon dioxide) or chronic (gradual accumulation of carbon dioxide in the air).

However, the ability of man to consciously distinguish an admixture of carbon dioxide in inhaled air has had very little special study. On that count, only incidental observations are cited in the literature.

Schmidt (1956) has shown that the first unpleasant sensations in man developed only when the carbon dioxide content in a respiratory mixture reached 6% or even more. Cutler et al (1964) exposed people in an altitude chamber. During the first four days the gas medium was almost free from any admixture of carbon dioxide. Then a 3% admixture of that gas was added to it. The hypercapnic medium was maintained in the chamber for the next four days. Although the subjects did not know exactly when the carbon dioxide was added to the atmosphere of the chamber, they agreed with one another in noting changes of the medium. However, they made mistakes about the time. The predominant reference point for the people in the experiment was hyperventilation, sometimes headache. They noted these symptoms more frequently on the 2-3rd day of exposure. The latter sensation was lessened by increased ventilation; some people experienced it intermittently. This sensation disappeared if the person's attention was distracted. Therefore, many of the subjects assumed that the carbon dioxide was given intermittently. The authors came to the conclusion that man's ability to determine such quantities of carbon dioxide in the atmosphere is unreliable.
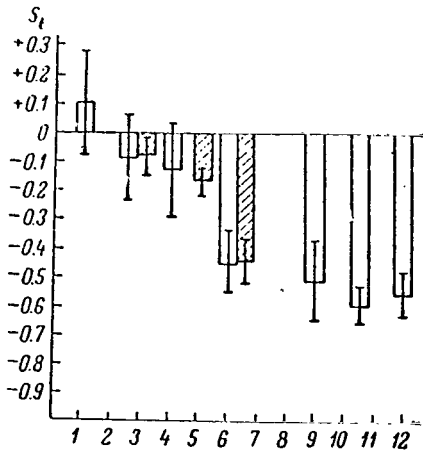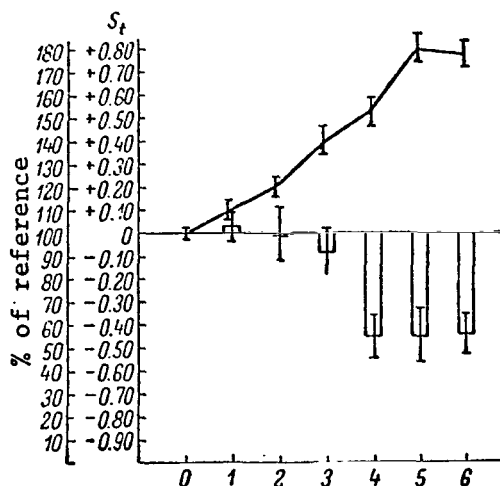
Figure 14. Hypercapnic gas preference of man. Average data from 24 subjects.
Horizontally - percent of carbon dioxide in the differentiated mixture. The rest of the legend is the same as in Figure 7.

In our experiments, (Breslav and Salatsinskaya, 1967a) we determined the gas preference of man with respect to hypercapnic mixtures (from 1 to 6% CO_2) with normal oxygen content.

In a five-minute period of a given respiration (Figure 14) a man did not distinguish mixtures with 1-2% CO_2 from air, although increased ventilation was already noted. When the admixture of carbon dioxide in the differentiated mixtures reached 3-4% or more, the subjects displayed a negative response, mostly citing labored or strenuous breathing. Similar sensations could appear beginning with the end of the first or with the second minute of inhaling the mixture.

One of the groups of subjects was exposed to hypercapnic media, not only   /50
for five minutes, but also for 10 and 15 minutes. We shall discuss how under these conditions the man's reactions changed when inhaling the two mixtures: threshold with respect to distinction (3% CO_2), and clearly above threshold (5% CO_2) (Figure 15).

The mixture containing 3% CO_2 caused an increase of pulmonary ventilation, which continued until the 10th minute. The shift of alveolar P_{CO_2} appeared to be approximately the same in the 5-minute as well as the 10- and 15-minute inhalations. At the same time a negative attitude of the subjects to the 3% admixture of CO_2 was only reliably revealed with the 10- and 15-minute period of a given respiration.

In inhalation of mixtures with 5% concentration of carbon dioxide, shifts of these indicators were expressed much more strongly. In particular, the
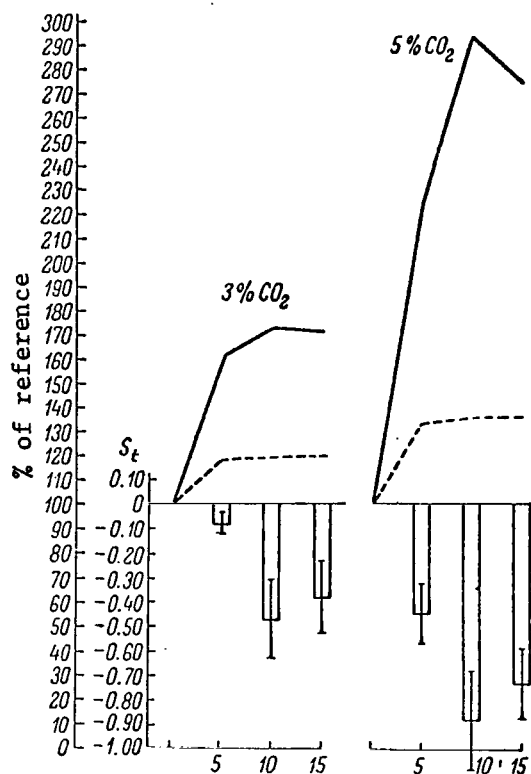
Figure 15. Responses of man to hypercapnic mixtures in various lengths of breathing time. Average data from 12 subjects.
Broken line — alveolar P_{CO_2}.

Horizontally — length of periods breathing a given mixture (in min). The rest of the legend is the same as in Figure 7.

content of carbon dioxide in the alveoli increased considerably. Avoidance of the hypercapnic medium was observed here even in the 5-minute period of a given respiration (Figure 16). In experiments with more prolonged inhalation of this mixture, it was rejected in all cases.

Here, as also in responses to hypoxic media, the significance of the time factor was displayed. A 10-minute period of inhaling a 3% admixture of carbon dioxide was necessary for a significant negative choice to be displayed. But a 5-minute inhalation was sufficient for a clear response to 5% CO_2. Such an increase in the /51 ability to distinguish excess carbon dioxide during extended exposure can be explained by an intensification of hypercapnic shifts in the organism. Actually, on inhalation of carbon dioxide mixtures, alveolar P_{CO_2} remained at a constant level to the 5th minute, but ventilation in longer respiration of the mixtures continued to increase somewhat. This indicates subsequent intensification of hypercapnic stiumulation.

Hyperventilation, or more accurately, the expenditure of energy connected with it in the extra work of the respiratory muscles, can also be one of the factors in an organism's negative response to excess carbon dioxide. This will be discussed in more detail·in Chapter IV. In fact, the choice index of hypercapnic mixtures in our experiments was correlated to approximately the same /53 degree both with the alveolar tension of carbon dioxide (which to a certain
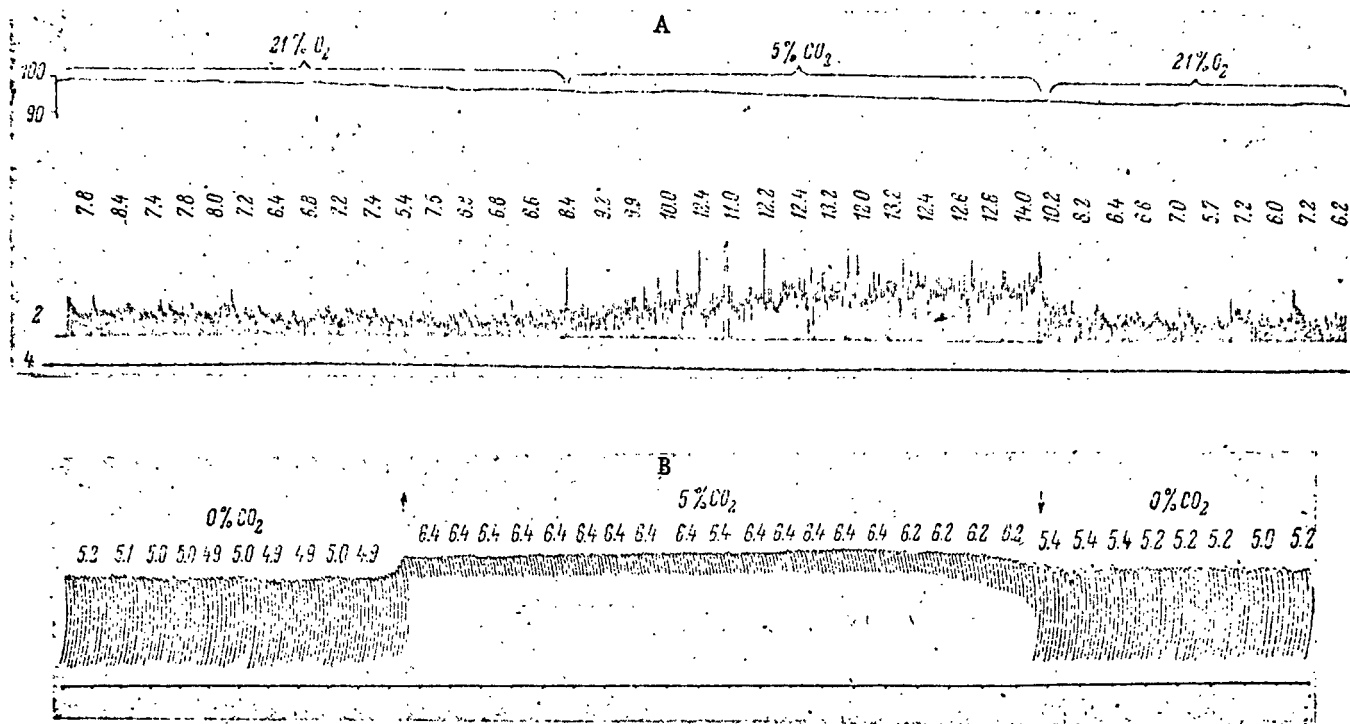
Figure 16. Man's respiration of air and a hypercapnic mixture.

A - spirogram; the legend is the same as in Figure 8;
B - capnogram: the peaks reflect alveolar carbon dioxide content;
time - 1 minute. Read from right to left.

extent reflects arterial P_{CO_2}), and with the increase of volume of respiration per minute in inhalation of these mixtures (corresponding correlation coefficients were -0.93 ± 0.18 and -0.95 ± 0.16).

Therefore, man (an probably animals, too) distinguish an admixture of carbon dioxide in a medium when compensation for increased partial pressure is disturbed or accompanied by significant hyperventilation.

HYPOXIC MEDIUM WITH INCREASED CARBON DIOXIDE CONTENT

The relative influence of the effects of insufficient oxygen, on the one hand, and excessive carbon dioxide on the other, has an exceptionally complex character. Its analysis is important both theoretically and practically.

The hypoxic-hypercapnic interaction is extremely important in regulating respiration. Exactly such an interaction takes place in muscular activity. Therefore, the combined influence of insufficient oxygen and excess carbon dioxide must be a more adequate stimulus for the organism than each of these factors separately.

In the thirties, it was noted that if increased carbon dioxide content in an inhaled gas mixture acted on the background of decreased partial pressure of oxygen, then the total ventilator response is especially signficant (Henderson and Randolf, 1932, cited by: Cordier and Heymans, 1935; Haldane and Priestley, 1935, et al).

Much consideration has recently been given to this phenomenon in the physiology of respiration. It has been established that hypoxia lowers the threshold of ventilator response to carbon dioxide (Saito et al, 1960; Honda et al., 1963; Tenney, 1963; Wiemer, et al, 1963; Archibald, 1964, Salzano and Hall, 1965; Malmejac, et al., 1966; Honda, 1968), and also increases VRM in inhalation of a hypercapnic mixture (Bourverot et al., 1963, 1965; Michel and Milledge, 1963; Cunningham, et al., 1964), and accelerates the onset of this

response (Mallie-Colard, et al., 1965; Bernards, et al., 1966). The slope curve of VRM/arterial P_{CO_2} increases. As a result, the total ventilator response to hypoxia combined with hypercapnia exceeds the arithmetical sum of the effects of these two factors acting separately (Nielsen and Smith, 1951; Cormack, et al., 1957; Lloyd, et al., 1958; Lambertsen, et al., 1963, and others). On the other hand, hypoxic responses appear more clearly on a background of hypercapnia (Petrov, 1949; Strumza, 1966, et al). In addition, a specific level of carbon dioxide in the internal medium seems a necessary condition for the organism in general to react to hypoxic stimuli. Thus, VRM increases with an insufficiency of oxygen in inhaled air in man only if P_{CO_2} of not less than 30 mm Hg is maintained in the blood (Nielsen and Smith, 1951).

Let us add that under hypoxic conditions hypercapnic action is favorably expressed because of the local vessel-dilating effect of carbonic acid which improves the blood supply of vital organs — the brain and myocardium (Sanotskaya, 1962, et al).

In view of what has been said, we can consider valid the suggestion to reduce the oxygen content in inhabited dwellings where carbon dioxide accumulation is possible: slight hypoxia should promote a strong response to hypercapnia and facilitate the removal of carbon dioxide (Puccinelli et al, 1964; Strumza, 1964). The favorable influence of carbon dioxide in hypoxia is also of practical importance. This consists of preventing the harmful aftereffects of hypocapnia, developing from hyperventilation (Shick, 140; Asmussen, 1965, et al.).

Excess carbon dioxide is also positively expressed in the blood supply and oxygen regime of such vital organs as the heart muscle and brain (Sanotskaya, 1962a, 1962b; Kovalenko, 1964; Wiljelm, 1966).

Here, however, we must take the following facts into account:

(1) It is possible for exceedingly acute anoxia (respiration of mixture

with 8% O_2), instead of intensifying, to depress responses to carbon dioxide (Purves, 1966). Inhalation of very high (more than 6%) concentrations can lead to weakening or even loss of response to hypoxia (Wiemer, et al., 1963). Actually, these phenomena are connected with depression of the nerve centers in extreme hypoxia or hypercapnia (Balakhovskiy, 1952; Yu. N. Ivanov, 1961; Dolina, 1965, et al.).

(2) Increased alveolar pressure of oxygen, the result of strong ventilator response with combined hypoxia and hypercapnia, does not much increase the oxygen supply to the tissues, if we take into account the increase of energy expenditure in respiration and the influence of the Bohr effect on the dissociation curve of oxyhemoglobin (Strumza, 1966).

It appears to us that comparative analysis of the active choice responses to corresponding mixtures by animals and man could help in the physiological evaluation of one or another combination of oxygen deficiency and excess carbon dioxide in a respiratory medium.

Hypoxic-Hypercapnic Gas Preference in Animals

We conducted experiments on rats to study behavioral responses to a medium where the oxygen content was lowered and the carbon dioxide concentration was increased at the same time. An ordinary air atmosphere was maintained in the undifferentiated zone of the gas gradient instrument. In the differentiated zone, the medium had the following composition: 12% O_2, 3% CO_2, 85% N_2.

It has been shown above that both factors operating here (the lowering of the content of O_2 to 12% and the 3% admixture of CO_2), taken separately are over-threshold factors in relation to the gas preference of rats and do not give a statistically significant choice. But the combination of these same factors caused a distinct avoidance response. The intensity of this response clearly exceeds the arithmetical sum of responses to the same degree of hypoxia
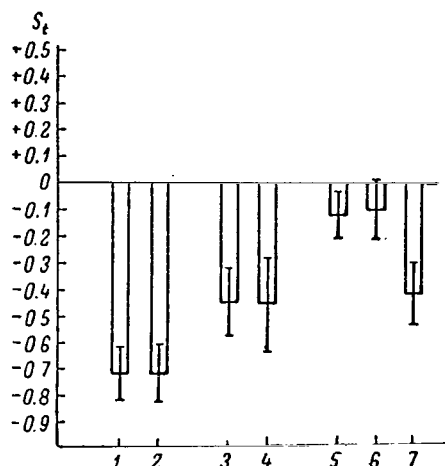
Figure 17. Hypoxic-hypercapnic gas preference in rats. Average data from 20 animals.

Vertically – choice index for the differentiated zone (S_t);

Horizontally – composition of the medium in the differentiated zone: 1 – 7% O_2; 2 – 7% O_2 in a background of 3% CO_2; 3 – 9% CO_2; 4 – 9% CO_2 in a background of 11.5% O_2; 5 – 3% CO_2; 6 – 12% O_2; 7 – 12% O_2 + 3% CO_2

and hypercapnia, acting separately (Figure 17, 5-7). Such a mutually-intensifying effect of local oxygen deficiency and excess carbon dioxide corresponds to the analogous activity of a given combination in a respiratory response.

In another series of experiments, a more stringent differentiated medium was created: 6% CO_2 and only 2% O_2. But instead of increasing the effect, the opposite result was obtained. Having entered such an atmosphere, the animals as a rule did not display any expressed motor response and died from the effects of acute oxygen starvation (cramps, stoppage of breathing). Evidently the combination of pronounced anoxia and significant hypercapnia causes extreme repression of the functions of the central nervous system, and behavior response seemed to be paralyzed.

Experiments were also conducted where a moderately hypercapnic mixture (3% CO_2) was maintained along the whole length of the gas gradient instrument. The oxygen content in the undifferentiated zone was normal (21%), but in the differentiated zone it was decreased to 7%. As seen in Figure 17, 1,2, the rats' negative response to the hypoxic medium was not distinguished, under these circumstances, from response to the very same medium when an admixture of carbon dioxide is lacking.

An analogous result was obtained when the background had a lowered (to 11.5%) oxygen content, and an increased (9%) carbon dioxide concentration was created (Figure 17, 3,4). Here the animals' negative preference to a hypercapnic medium was the same as with normal oxygen content.

60

Actually the organism adjusts successfully to an insignificant oxygen deficiency as well as to a small excess of carbon dioxide. Therefore, such a moderate shift in gas composition, if it is maintained the whole length of the gas gradient instrument, does not change the behavior responses of animals to local extremely hyperoxic or extremely hypercapnic media.

Hypoxic-Hypercapnic Gas Preference in Man

As with animal experiments, the basic variant of the experiments with people was a comparison of ordinary air and a respiratory mixture containing 12% O_2 or 3% CO_2 (Figure 18).

Ventilator response to such a mixture, as must be expected, exceeded the arithmetical sum of the separate effects of corresponding degrees of hypoxia and hypercapnia. Comparatively small shifts in the oxygenation of the blood and the alveolar pressure of carbon dioxide indicate good compensation for oxygen deficiency and excess carbon dioxide in a respiratory medium. Moreover, the subjects in only 5-minute exposures clearly avoided breathing a given mixture (choice index -0.37 ± 0.10), with a distinctness that was not observed when similar hypoxic (12% O_2) and hypercapnic (3% CO_2 in air) media were applied separately. The negative response was still clearer in 10- and 15-minute periods of a given respiration (corresponding choice indexes were -0.66 ± 0.14 to -0.70 ± 0.13), although physiological parameters remained almost the same.

To determine response to hypercapnia in a moderately hypoxic background in experiments with people, we used as an undifferentiated medium a mixture of 12% O_2 with nitrogen. As the differentiated medium we used mixtures with the same oxygen concentration containing a varying percentage of carbon dioxide.

As Figure 19 shows, ventilator response to an admixture of carbon dioxide on a background of insufficient oxygen does not essentially differ from that described above with a normal oxygen content. Avoidance response was already clear with 2.5% CO_2, i.e., the threshold for distinguishing a hypercapnic medium under hypoxic conditions decreased in comparison with conditions of normal /58
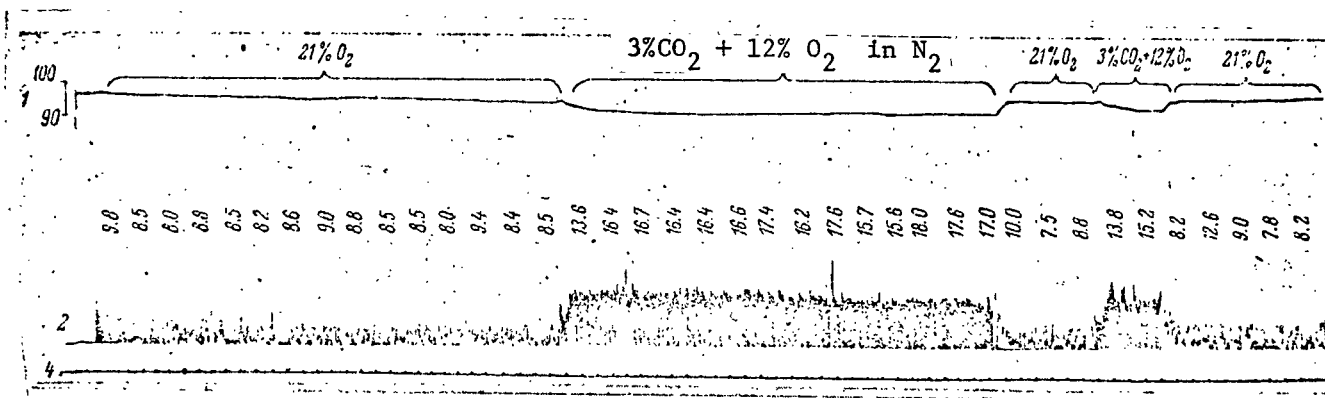
Figure 18. Man's respiration of air and hypoxic-hypercapnic mixture. Critical hyper-
ventilation. The legend is the same as in Figure 8.
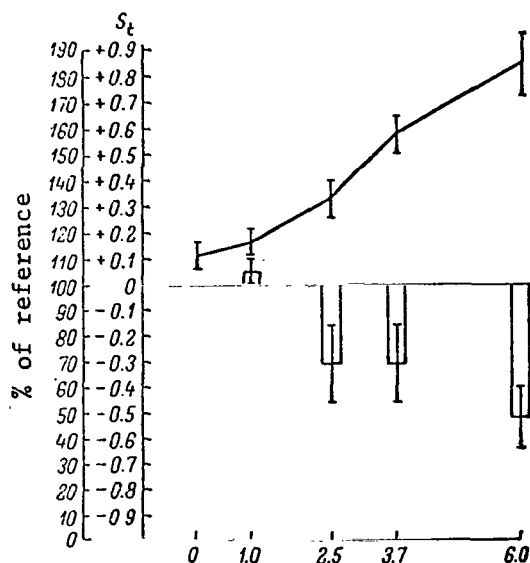
Figure 19. Hypercapnic gas
preference of man on a background of a lowered
oxygen content (12%). Average data from 12 subjects.
Horizontally – percent of
carbon dioxide in the differentiated medium. The
rest of the legend is the
same as in Figure 7.

oxygen content (where this threshold, let
us remember, was 3-4% CO_2). The increased
sensitivity to carbon dioxide in an hypoxic
background probably can be explained by the
somewhat higher VRM level during inhalation
of these mixtures.

Research of the opposite character has
also been conducted: the influence of small
admixtures of carbon dioxide on hypoxic responses has been studied. The subjects were
offered two mixtures containing 3.5% CO_2.
The undifferentiated mixture had a normal
concentration of oxygen; the differentiated
one had a lowered concentration (Figure 20).

It is clear that owing to the hypercapnic background, respiratory volume and
ventilation were already elevated. The
inhaling mixtures with 12 and 9% O_2, the
volume of respiration per minute and also
the frequency of heart contractions increased much less than under the influence of these same mixtures without the addition of carbon dioxide. The reduction of oxygenation of the blood was also much less.

Under these conditions the subjects did not distinguish a mixture contain- /59
ing 12% O_2 from the undifferentiated mixture. A negative response was exhibited
only for a mixture with 9% O_2.

The diminished influence of carbon dioxide on the negative response of
man inhaling hypoxic mixtures can be explained by the improved oxygenation of
the blood under the influence of hypercapnic hyperventilation which is recognized quite clearly.
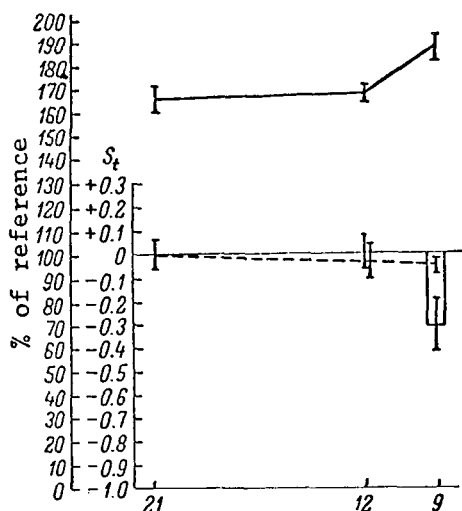
Figure 20. Hypoxic gas preference of man in a medium with added carbon dioxide (3.5%). Average data from 12 subjects. The legend is the same as in Figure 7.

The following circumstances could also take place. The undifferentiated mixture, containing exactly the same admixture of carbon dioxide as the differentiated one, already caused an increase of ventilation. Switching to the differentiated medium (with a lowered oxygen content) was not accompanied by any kind of significant increase in respiratory activity. This factor could not play a very large role in the distinction of gas mixtures by the subjects. It may also be important that an admixture of carbon dioxide keeps it from being excessively washed out of the organism (the removal being caused by the increased ventilation of hypoxia).

Wayne (1958) in altitude chamber experiments pointed out the similarity between the subjects' verbal reports about their sensations at an "altitude" of 7500 meters and indications by the very same people after arbitrary hyperventilation under ground conditions. The author explained this by the fact that oxygen starvation was also accompanied by hyperventilation. As he reasoned, this similarity can seriously hinder a pilot's recognition of his own hypoxic condition during a flight. /60

It must be assumed that at least part of the sensations which man uses to distinguish mixtures with lowered oxygen content are due to their hypocapnic origin. And if this is so, then such a distinction must actually be weakened when there is a background with a carbon dioxide admixture.

At the same time it must be stressed that depressed activity in critical degrees of oxygen deficiency and excess carbon dioxide can lead to lowering and even complete loss of an organism's ability to respond adequately to these factors. This has been shown in animal experiments.

Summing up the experimental data discussed here, we must assume that distinction by animals and man of gas mixtures with altered oxygen and carbon dioxide content (in the form of negative choice response) within known limits reflects both the shifts in an organism's gas regime which occur under the influence of these mixtures, and the effort expended in the mechanisms which compensate for these shifts.

Chapter III

RESPONSES OF THE ORGANISM TO GAS MEDIA CONTAINING HELIUM

Up until now, we have been concerned with oxygen and carbon dioxide as
agents participating in gaseous exchange; sometimes they are called "respira-
tory gases". But how does an organism perceive a physiologically neutral com-
ponent of a respiratory medium?

In this connection it seemed essential to us to explore the possible phys-
ical effect of substituting another gas — helium, for the natural diluent of
oxygen — atmospheric nitrogen.

Although helium is found in trace amounts in the Earth's atmosphere
(0.00053%), physiologists have become much more interested in this inert gas in
the last ten years. Helium has a number of remarkable properties. For many
reasons, it has been suitable to introduce helium as an oxygen diluent for
divers. In particular helium is almost seven times less dense than nitrogen
(0.00018 g/cm^3). With the increased pressure in deepwater descents this con-
siderably reduces the energy expenditure which is connected with overcoming
the increased resistance of the respiratory medium (Behnke and Yarbrough,
1939; Orbely, et al., 1940; Marchall, et al., 1956; Lanphier, 1958; Kumanichkin,
1960; Zal'tsman, 1961; Wood and Leve, 1963; Albano and Ciulla, 1966; Brousseles,
et al; 1966).

For this same reason, attempts have been made (and are being made) to use
helium mixtures in clinics to alleviate respiration in people with obstructive
diseases of the respiratory organs (Barach, 1934, 1936; Green and Day, 1954;
Schiller, et al., 1955; Comroe, et al., 1956; Dembeau, 1957, and others).

Recently there have been lively debates on the question of the advisability of using helium in the composition of an artificial atmosphere for space flights (Dianov and Kuznetsov, 1963; Epperson, et al., 1965, et al). Besides lightness, the high thermal conductivity of this gas (at 20°C helium conducts $43 \cdot 10^4$ kcal/m·hr·g, and nitrogen only $15 \cdot 10^4$ kcal/m·hr·g) was considered, which could improve a cosmonaut's heat transfer if there were no convection deficiency in the cabin of a spaceship under weightless conditions. Other argu- /62 ments were also put forward in favor of creating a helio-oxygen atmosphere in manned space vehicles.

From this the question arises: can an organism exist long in conditions where nitrogen is completely or partially replaced with helium? However, a number of experiments have shown that neither lack of nitrogen nor possible physiological influence of helium itself has caused any ill effects on the organism of animals or people exposed to a helio-oxygen medium for many days and weeks (Bond, 1963; Wright et al., 1964; Bartek et al., 1966; Hamilton et al., 1966; Left et al., 1966; Robertson et al., 1966). It must be taken into consideration that, because of the high heat-conductivity of helium, a higher temperature must be maintained to preserve thermal comfort (Leon and Cook, 1960; Boriskin et al., 1963; Troxhikhin, 1966; Epperson et al., 1966; Fox, et al, 1966: Bonura et al.; 1967).

Thus, helium mixtures probably have greater promise as an artificial respiratory medium.

At the same time, responses of an organism to respiration of such mixtures have not been studied very much as of yet. The application of the gas preference method could partly fill in some of the gaps in our knowledge about the physiological effects of helium.

In this part of the research, we tried to answer two questions:

(1) Do animals·and man distinguish (and how) mixtures containing nitrogen and helium as diluent?

(2) Do gas preference responses to altered oxygen and carbon dioxide
       content in a helium medium change (and in what direction)?

<u>GAS PREFERENCE IN ANIMALS UNDER CONDITIONS OF NORMAL AND DECREASED</u>
<u>OXYGEN CONTENT</u>

We (Breslav, et al., 1965) conducted experiments with animals where an
air mixture (nitrogen-oxygen) was supplied to the undifferentiated end of the
gas gradient instrument and a helio-oxygen mixture (79% He + 21% O_2) to the
differentiated end.

Under ordinary temperatures, white mice avoided the helium zone (Figure
21). Such a reactions could have been caused by the mentioned cooling effect
of the helium medium. We attempted to supply a helio-oxygen mixture that was
somewhat heated in comparison with the air mixture. This was accomplished by
passing the mixture through a coil mounted in a water ultrathermostat. The
temperature in the chamber of the gas gradient instrument was controlled by an
electrothermometer which was connected to both ends of the chamber.

Actually, raising the temperature of the helium-oxygen mixture by only 0.5°
completely eliminated any negative response of the animals to the helium
medium.   <u>/63</u>

In connection with this, it was decided to find out what the temperature of
the helio-oxygen mixture must be so that the animal's heat exchange conditions
in this medium would be the same as in an ordinary air atmosphere. Y.A. Konza
(1965) conducted special research in our laboratory. As is known, one of the
most important indications of thermoregulation is the "critical point". This
is the temperature zone in which an organism's expenditures of energy to pre-
serve a heat balance are minimal and, consequently, exchange is at the lowest
level. In small warm-blooded animals (mice, for example) the critical point
in an air medium is approximately 30° (Herter, 1936; Slonim, 1952). Thermal
effects noticeably deviating from this point lead to increased exchange
(Starkov, 1961; Gubler, 1962, et al.). In Konza's work the thermal regulation
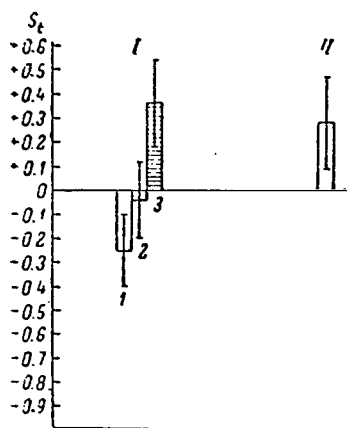
Figure 21. Helium gas preference of mice in a medium with a normal (I) and lowered to 7.5% (II) oxygen content. Average data from 20 animals. 1 - even temperature in both mixtures; 2 - helium mixture heated to 0.5°; 3 - heated to 3.0°. Horizontally - choice index of helium-oxygen mixture in comparison with nitrogen-oxygen mixture (S_t).

of the animals was indicated by oxygen consumption and rectal temperature. Oxygen consumption was determined by using two gas exchange instruments at once: in one, the animals were in an air atmosphere, in the other they were in a helio-oxygen medium (21% O_2 + 79% He). Rectal temperature was measured by an electrothermometer. An ultrathermostat under the control of an electro-thermometer was used to create and maintain the necessary temperatures in the chamber. Comparative studies were made on thermoregulation of white mice in temperature media of 16, 20, 25, 30, 35, and 40°C. Comparison of oxygen-consumption in the helio-oxygen and air media shows that at 30° and below the exchange level of mice is higher in the helium medium than in the air medium (Figure 22). The cooling effect of the helium was reflected in the animals' rectal temperature. Calculations based on the data we obtained show that the temperature of the critical point (i.e., the thermal neutral zone) for mice in a helio-oxygen medium is 3-4° higher than in an air medium. It lies between 33-34°.

Having determined this fact, we conducted experiments in the gas gradient instrument, heating the helio-oxygen mixture so that it was 3° warmer than the air. In this experiment the animals displayed a distinct preference for the helio-oxygen medium in comparison with ordinary nitrogen-oxygen (Figure 21). Thus, when thermal exchange conditions are equalized, the animals choose the medium where nitrogen is replaced with helium.

It turned out that if the nitrogen and helium mixtures contained a decreased (but equal) concentration of oxygen (7.5%) (Figure 21), the mice clearly preferred the helium end of the gas preference instrument. This was in spite of

the fact that both mixtures in a given series of experiments had the same temp-
erature. It would seem that the helium mixture would have a cooling influence
on the animals, especially as the helium content in a hypoxic mixture is higher
than in the normal mixture. Moreover, with conditions of oxygen starvation,
as was mentioned in Chapter II, gaseous exchange (and this means heat produc-   /64
tion, too) in animals drops; such cooling in the helium medium is expressed
particularly sharply (Altland, et al., 1968).

These facts indicate that some characteristic of helium cause the animals
to prefer, especially in hypoxic conditions, the helium medium to the usual
nitrogen one. It can be assumed that these characteristics have a specific
influence on the respiratory function and will have to be studied in experiments
on man.

GAS PREFERENCE IN MAN UNDER CONDITIONS OF NORMAL AND DECREASED
OXYGEN CONTENT

The high heat conductivity of helium is not of vital importance for · ⌐
in breathing gas mixtures through a mask. This was shown in experiments ˅
Bowers and Fox, 1967 . The cooling effect of such a medium is detected ˍ
people in a helio-oxygen atmosphere. If a man only breathed the helio-uₓyₒ   · ˅ ⌐
mixture through a mask and remained in an ordinary air medium, his heat ex-
change did not change. Therefore, in our experiments we were able to trace the
physiological influence of other characteristics of helium not connected with
its thermal conductivity.

How did man respond to the substitution of helium for nitrogen? The sub-
jects were offered two respiratory mixtures containing the same percentage of
oxygen, a nitrogen mixture (undifferentiated) and a helium mixture (differen-
tiated). The helium mixture caused a small increase in the frequency of res-
piration with corresponding decrease of respiratory volume (Table I). This
developed as an adaptation to a less dense respiratory medium. Under these
conditions frequent and shallow breathing is more economical (Comroe, et al.,
1956; Schilder, et al., 1963; Trumpayts and Kaminskiy, 1967). An analogous
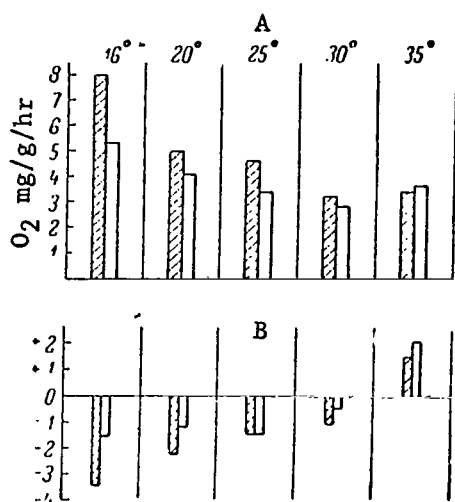
Figure 22. Oxygen consumption (A) and rectal temperature (B) of mice at the end of a half-hour exposure to a nitrogen-oxygen (white column) and helium-oxygen (shaded column) atmosphere at various temperatures of the medium. Average data from 20 animals (according to Konza, 1965).

phenomenon can also be noted in breathing hypoxic helium mixtures, although the observed shifts are not always statistically reliable. Oxygen saturation of the blood hardly depended at all on whether the man breathed a helium or nitrogen mixture.

Under both normal and hypoxic conditions, the subjects invariably gave their preference to the helium mixtures in comparison with the nitrogen mixtures.

The reason for this probably involves the decreased respiratory work demanded to support necessary alveolar ventilation in a less dense helium medium in connection with lowered resistance of the gas flow in the respiratory passages (Barch, 1936; Grafe, et al., 1960). Behnke and Yarbrough (1939) have found that in atmospheric pressure replacing nitrogen with helium does not change the sensations in divers which depend on resistance to respiration. However, model experiments of these same authors have shown that under conditions corresponding to forced breathing the resistance to breathing helio-oxygen mixtures in narrow tubes is one and a half times less than the resistance to breathing air under these conditions. This problem is complicated by the fact that, in the presence of a laminar flow in a smooth tube, helium does not decrease, but increases resistance, because it has a greater viscosity than nitrogen. But it must be kept in mind that in the branchings of the tracheobronchial tree there is a vortex, and it is here that the density of gas assumes a decisive role: with its decrease, resistance to flow drops sharply.

Let us recall that resistance to gas flow in the respiratory tracts is expressed by the ratio

$$\Delta P = k_1 \cdot \dot{v} + k_2 \cdot (\dot{v})^2,$$

where ΔP is the pressure gradient in the respiratory passages; k_1 and k_2 are the constants corresponding to laminar and turbulent gas flows, the first constant reflecting the viscosity of the gas and the second its density; $\dot{v}$ is the volume of respiration per minute.

It follows from this that the specific gravity of the second component in the above formula increases when there is a turbulent flow, and consequently, the sum (ΔP) expressing flow resistance decreases significantly with low gas density. If the volume of respiration per minute is increased, the turbulence of the gas flow in the respiratory passages increases. Under these conditions, the alleviating influence of helium on respiration ought to become more pronounced, especially as the value of the turbulence constant, (i.e., gas density) which corresponds to the above formula increases proportionally to the square of ventilation. This reasoning is confirmed by the fact that during muscular effort breathing helio-oxygen mixtures is more effective (Kulik, 1967).

In the preceding experiments (Breslav and others, 1965) we learned that in return respiration in a closed chamber filled with a helio-oxygen mixture, man successfully "reached" a lower oxygen content in the respiratory medium. Hypoxia caused, in the words of the subjects, fewer unpleasant sensations than were observed with the nitrogen-oxygen medium. In spite of the fact that the oxygen content in the helium medium is lower than in the nitrogen medium, oxygenation of the blood at the end of the experiment in both cases hardly differs at all. This fact can also be considered as a consequence of more effective alveolar ventilation in breathing helium mixtures. As helium facilitates the movement of gas mixtures in the respiratory passages, primarily the proximal passages (Barnett, 1967), alveolar ventilation in breathing helio-oxygen mixtures is attained with less respiratory muscle work because of the lowered resistance to the gas flow.

The work of Wiley and Zechman (1966/1967) shows that man perceives a difference in respiration resistance of only 0.5 - 1.0 cm water/ℓ/sec. Response

TABLE   1

RESPONSES OF MAN TO NITROGEN AND HELIUM RESPIRATORY MIXTURES WITH NORMAL AND
LOWERED OXYGEN CONTENT.   AVERAGE DATA FOR 12 SUBJECTS

Mixture used	Parameters of respiration & oxygenation of blood during inhalation of mixtures & their differences (D ± m)				Choice index of helium mixture (S_t)	Number of subjects (%)	
	rhythm of respiration in min.	min. vol.of resp., liters	resp.vol, liters	oxygen saturation of blood, %		selecting a mixture	not making a choice
with 21% O_2							
nitrogen	17.0	6.8	0.40	93.3	—	17	8
helium	17.6	6.5	0.38	92.2	—	75	
D±m	+0.6±0.3	−0.3±0.2	−0.02±0.01	−1.1±0.9	+0.33±0.14	—	—
p	0.05	0.2	0.01	0.2	0.05	—	—
" 18% O_2							
nitrogen	16.6	6.9	0.42	91.0	—	33	8
helium	17.6	7.0	0.40	91.2	—	58	
D±m	+1.0±0.3	+0.1±0.3	−0.02±0.01	+0.2±0.5	+0.33±0.13	—	—
p	0.01	>0.5	0.05	>0.5	0.01	—	—
" 15% O_2							
nitrogen	16.8	7.4	0.46	86.3	—	25	8
helium	17.0	7.2	0.42	86.5	—	67	
D±m	+0.2±0.4	−0.2±0.3	−0.04±0.02	+0.2±0.5	+0.27±0.11	—	—
p	>0.5	0.5	0.05	>0.5	0.5	—	—
" 12% O_2							
nitrogen	15.9	7.6	0.49	83.2	—	17	8
helium	16.6	7.4	0.46	83.6	—	75	
D±m	+0.7±0.5	−0.2±0.4	−0.03±0.02	+0.4±0.9	+0.22±0.09	—	—
p	0.2	>0.5	0.2	0.3	0.05	—	—
" 9% O_2							
nitrogen	16.3	10.5	0.67	79.3	—	25	8
helium	18.0	9.9	0.57	79.4	—	67	
D±m	+1.7±0.8	−0.6±0.4	−0.10±0.04	0.0±1.5	+0.21±0.10	—	—
p	0.05	0.3	0.02	—	0.05	—	

to a changed resistance does not depend on how it is created (general pressure of the medium, density of the gas mixture) (Maio and Fahri, 1967). Incidentally, this is the basis for divers' ability to determine by their own sensations their submersion depth. We will discuss here distinguishing the density of a medium. If a dense gas — argon — is included in the composition of a respiratory medium, the diver subjects give an exaggerated estimate of their depth (Behnke and Yahrbrough, 1939). At the same time, the organism tends to select those conditions in which there would be the least respiratory work (Comroe, et al., 1956; Gray and Field, 1959, et al).

We suggest that just for this reason both animals and man display a positive response to gas mixtures where helium is used as a diluent of oxygen. Verbal indications of the subjects verify such a supposition. They evaluate helium mixtures as "easier" to breathe.

HYPOXIC AND HYPEROXIC GAS PREFERENCE

Let us consider the question of how the substitution of helium for nitrogen influences an organism's responses to hypoxic respiratory media.

The responses of white mice, under conditions of such an exchange, to a mixture containing 12.5% O_2 are approximately the same as in a nitrogen medium.

In experiments on people (Breslav and Salatsinskaya, 1966, 1967), the subjects were divided into two groups: one breathed only nitrogen mixtures during the experiments, the other — only helium mixtures. The undifferentiated mixture in each experiment was a mixture with a normal oxygen content; the differentiated mixture had a lowered content.

As seen in Figure 23, the subjects did not distinguish between a mixture of nitrogen with 18% O_2; this was shown in Chapter II. The analogous helium mixture was mostly preferred in comparison with the undifferentiated mixture, in spite of the fact that oxygenation of the blood was already lowered. It may be inferred that such a mixture, because of the small supplementary hypoxic

Figure 23. Hypoxic gas preference of man in a nitrogen (I)
and in a helium (II) medium. Data from 12 subjects. The
rest of the legend is the same as in Figure 7.

stimulus, produces a more usual load on the respiratory appartus in man than
the helium mixture with normal oxygen content. Judging by the verbal reports
of the subjects, breathing the helium mixture seems unusually easy.   /69

Beginning with 15% oxygen content in a nitrogen mixture, ventilation in-
creases almost linearly depending of the degree of decrease of the oxygen con-
tent. In the helium group this relationship was more weakly expressed, even
though oxygenation of the blood in this group was decreased almost as much as
in the nitrogen group (distinction was in no way statistically significant).
Judging by selection response, the subjects did not distinguish a helium mix-
ture with 12% O_2 from the undifferentiated mixture, possibly in connection with
less increase of ventilation in breathing this mixture. At the same time, the
nitrogen mixture with 12% O_2 was avoided.

In more severe hypoxia (9% O_2) the difference between the groups disappeared
according to all indications. In particular, the clear negative response of the
subjects was the same both for the nitrogen and for the helium mixtures.

Therefore, in a helium mixture man's negative response to a medium degree
of hypoxia disappears, probably because of helium's favorable action on the

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Figure 24. Hyperoxic gas preference of man in a nitrogen (I) and in a helium (II) medium. Data from 12 subjects. The rest of the legend is the same as in Figure 7.

Experiments were also performed in which a man was presented with a choice between a normally oxygenated helio-oxygen mixture (21% O_2 + 79% He) and almost pure (98%) oxygen.

Under these conditions, the subjects as /70 a rule preferred to breathe the helium mixture, rejecting the oxygen (Figure 24). Such a result, of course, is not unexpected, as there are two reasons for this: (1) the factors which usually cause the majority of people to avoid breathing pure oxygen (see Chapter II) and (2) the great difference in density of both respiratory media (the density of oxygen is 0.0014 g/cm^2, i.e., still higher than nitrogen), which is why the ease of breathing the helium mixture in comparison with the oxygen appears even clearer. The subjects in fact indicated in their verbal report that it is more difficult to breathe oxygen.

HYPERCAPNIC GAS PREFERENCE

In this series of experiments conducted on people, the undifferentiated mixture was a helium or (as a control) a nitrogen mixture with normal (21%) oxygen content. Mixtures with the addition of various concentrations of carbon dioxide were also used as differentiated mixtures. As in the previous series, one group of subjects exclusively received nitrogen mixtures and the other received helium.

Ventilator response to carbon dioxide was expressed in the helium medium /71 more than in the nitrogen (Figure 25). This agrees with the data presented by Tenney (1964) and can be explained by the already cited alleviating action of
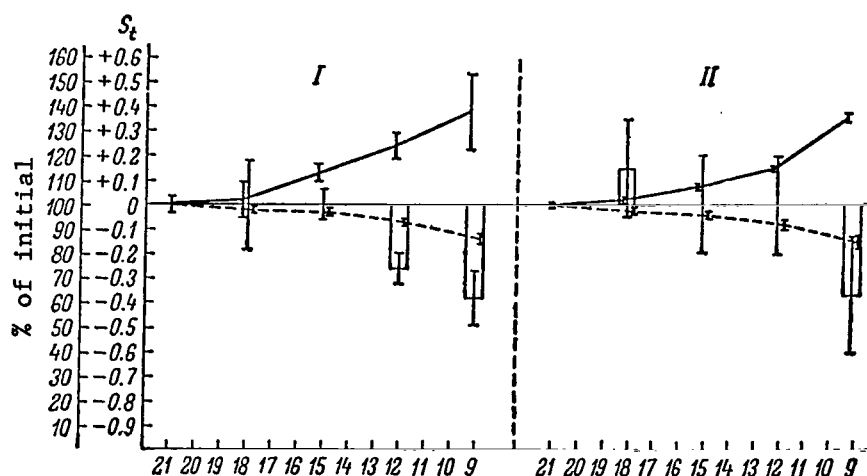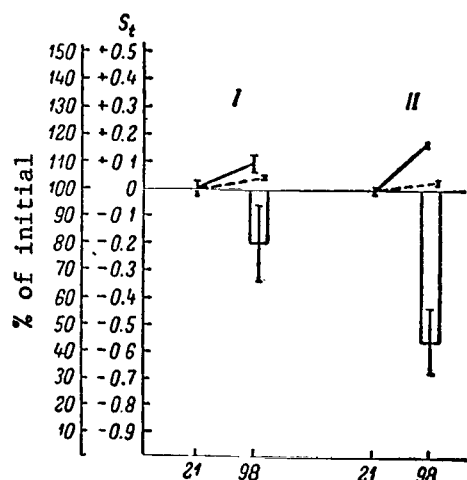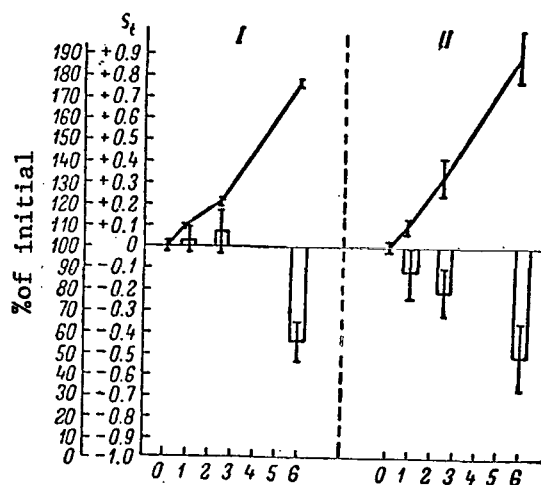
Figure 25. Hypercapnic gas preference of man in a nitrogen (I) and in a helium (II) medium. Data from 12 subjects. The rest of the legend is the same as in Figure 7 and 14.

helium on respiration with increased ventilation. The subjects even preferred somewhat the weakly hypercapnic (1% CO_2) helium mixture to the undifferentiated mixture. This, in an analogy with a weakly hypoxic mixture, might depend on the more "comfortable" character of breathing under conditions of a supplementary (in this case hypercapnic) stimulus. But a clearly negative response was noted to a mixture with 2.5% carbon dioxide content in the helium group, whereas there was no such response in the nitrogen group. The mixture containing 6% CO_2 was also clearly avoided in the nitrogen medium, but it was expressed more in the helium medium.

Medium degrees of hypercapnia in a helium medium seem to be better distinguished by man than in a nitrogen medium. This causes a more often expressed negative response. We assume that the combination of hypercapnia and the substitution of helium for nitrogen, because of its unusual nature, is not able to cause an adequate enough (in the sense of an agreement between increased ventilation and lung perfusion) compensation for the organism's response. This could cause noncompensatory hypercapnic shifts. In fact, this appears to be the reason for man's negative response to moderate hypercapnia. Direct research can definitely determine the carbon dioxide pressure in the blood in the respiration of corresponding mixtures.

*   *   *

It can be concluded from the data presented that the physical properties of helium are revealed in the distinction by animals and man of respiratory media which contain this gas. Among its most important properties are its low density, which facilitates decreasing the resistance of the gas flow in the respiratory passages, and its somewhat changing respiration regime.

The facts obtained confirm that on a number of occasions the use of helium mixtures can favorably influence man's respiration. It must be admitted that there are sufficiently valid recommendations for the use of a helio-oxygen mixture not only for the treatment of those with various air flow obstructions in the respiratory passages (Barach, 1934; Green and Day, 1954; Marshak, 1961; Kulik, 1967, et al), but also under several hypoxic conditions (Kane, 1940; Dolina, et al., 1966). The basic positive property of helium under these conditions is its favorable influence on the efficiency of respiratory muscle work.

Besides, several authors (Dembeau, 1957; Isayev, 1968) see an advantage in the great diffusion capacity of helium. Molecules of this gas, easily penetrating into the air passages, must, from this point of view, carry away molecules of oxygen. This improves pulmonary gaseous exchange conditions. As much /72 evidence as there is in the literature, the interesting hypothesis that — in respiration of helio-oxygen mixtures — gaseous exchange and the carbon dioxide diffusion ability of the lungs do not change still lacks experimental support (Robertson, et al., 1966). Our experiments did not show any specific influence of helium on the oxygenation of the blood, which would be impossible to explain by the changes of the breathing conditions discussed above.

Regarding the question of distinction by animals and man of respiratory media, the following important fact must be noted here. Experiments with helium mixtures clearly show that gas preference responses cannot only be determined by direct "chemical" influence of a certain mixture on the gas regime of an internal medium. Selecting a specific gas mixture, the organism also "takes into consideration" the greater or lesser ease of achieving a compensated gas regime. More accurately, it "considers" the energy expenditure in respiratory work which will guarantee the necessary alveolar ventilation under given conditions.

Chapter IV

RESPONSES TO THE ALTERED GAS MEDIUM UNDER FIXED BREATHING
REGIME CONDITIONS

Here we are going to discuss the question of what the organism uses as a
reference point in choosing and distinguishing gas mixtures.

Earlier we made the suggestion that, in actively choosing respiratory media
with varying oxygen and carbon dioxide content, an organism avoids most of all
those mixtures which cause in him uncompensated shifts of the gas regime (hy-
poxia, hypercapnia). Behavior of animals and man is determined by chemical
factors.

On the other hand, experiments with helium mixtures also demonstrated the
role of the respiratory muscle load as a factor which has an influence under
certain conditions on the choice by animals and man of certain gas media. It
is also impossible to deny the role of that factor in the mechanism of disting-
uishing hyperoxic and especially hypercapnic mixtures, as responses to the
latter can cause a significant increase in pulmonary ventilation. The mechan-
ical work of the respiratory muscles increases in hyperventilation to an even
higher degree than the volume of respiration per minute (Otis, et al., 1950).
Thus, hypercapnia increases energy expenditure in respiration particularly
sharply when the carbon dioxide content in the inhaled air exceeds 5% (Whitten-
berger, 1962). If the work of the respiratory muscles in quiet air breathing
is 0.56 kgm/min, then under the influence of hypercapnic mixtures this work in-
creases according to the P_{CO_2} proportionally to the logarithm of ventilation
for an exponent of 1.79 (Flenley, 1964). Cases are known in clinical practice
when an organism "tolerates" a certain degree of hypoxemia and hypercapnia to
avoid an increased respiratory load (Gray and Field, 1959; Shick, 1963).

However, in our experiments the threholds of ventilator response and distinction of respiratory mixtures often did not coincide. The selection index and the intensity of hyperventilation in breathing these mixtures are not always sufficiently clear. Therefore, it is difficult to imagine that man distinguishes specific media from air by his own respiratory responses. These verbal reports of the subjects about an apparent difficulty of breathing must be considered critically, as they are in no way connected with the expression of hyperventilation by a certain person. It is known that a self-report about the character of respiratory movements is achieved with great difficulty (Osipova, 1960). For example, people who were given a respiratory mixture containing 10.5% O_2 hardly noticed that their pulmonary ventilation at that time increased one and a half times (Voytkevich, 1952).

Nevertheless, what role do responses of the respiratory apparatus play in man's distinguishing and selecting gas mixtures? We conducted experiments where ventilator responses in breathing various mixtures were removed as far as possible (Breslav and Zhironkin, 1969). This was accomplished by fixing the breathing of the subject in a certain regime of rhythm and depth during the experiment. Respiration in man is closely connected with locomotor function and speech. Therefore, respiratory movements, as is known, can be controlled arbitrarily. This ability of man, studied recently by a number of authors (Smirnov, et al, 1962; Reid, et al., 1966/1967; Kulik, 1967; Fudin, 1967; Remmers, et al., 1968), is limited by demands to preserve an adequate gaseous exchange by the organism, (Danko, 1964; Kolyakina, 1967). Consequently the possibility of maintaining a normal respiration regime is connected, as is gas preference, with the physiological adequacy of an inhaled gas mixture. This stimulated us to study not only the distinction and choice of various mixtures under fixed respiration conditions, but also the limits within which man is able to inhibit arbitrarily ventilator response to changed composition of a respiratory medium.

To carry out these experiments, the spirographic apparatus described in Chapter I was fitted with a special attachment. A supplementary contact was mounted on each slide of the spirograph which slid along two vertical rods. The upper part of each rod was metal; the lower was covered with insulation.

The rod can be moved in a vertical direction, setting it at the proper level. The rods were activated by electric currents in series with signal bulbs (white and blue) on the panels of the subject and the experimenter. In the inhalation phase, the slide of the spirograph rose upwards, the sliding contact crossed from the insulated part of each rod to the metal part, closing the circuit of the corresponding bulb.

Before the experiment, the contact rods of both slides were set so that at each inhalation of the subject — at the moment when the minimum required respiratory volume was reached — the white light came on. When the inhalation reached the maximum allowable level, the blue one lit up. Each of the subject's inhala- /75 tions began on the stroke of an electric metronome, set at a certain rhythm. In advance two controlled experiments were conducted with each subject. In the first of these under free air breathing conditions, we found the natural volume and rhythm of respiratory movements for a given man. In the second experiment, the contact rods were set so that the white bulb came on when the respiratory volume of a given subject reached 90%, and the blue bulb when 110% was reached; the rhythm of the metronome was set to correspond with the respiration rate.

The subjects were given these instructions: breathe under the metronome, inhaling each time until the white bulb lights up and not allowing the blue one to be switched on. If the preset rhythm and depth of breathing were suitable, than all the subsequent experiments in a given series were conducted with this same regime, which, as a rule, the subject was quite used to.

HYPOXIC AND HYPEROXIC GAS PREFERENCE

Let us compare the data obtained in free breathing of hypoxic mixtures (Figure 7) with the results of the experiments conducted under fixed breathing regime conditions.

As is seen in Figure 26, with a constant ventilation level, the man displayed a clearer negative response to hypoxic medium. Such a response in a significant part of the subjects was already observed with 5-minute respiration
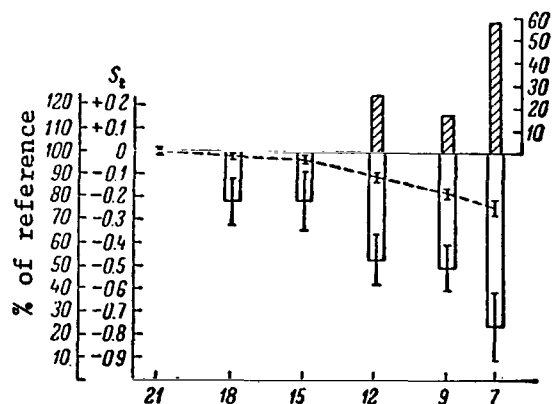
Figure 26. Hypoxic gas preference of man in fixed respiration regime conditions. Average data from 12 subjects. Shaded columns – number of "cutoffs" of a given respiratory volume (in % of the number of experiments). The rest of the legend is the same as in Figure 7.

of mixtures containing from 15 to 18% O_2, whereas in free breathing people usually could not distinguish these mixtures from air. Therefore, actual lack of hyperventilation during the respiration of hypoxic mixtures did not exclude the display of negative gas preference, but, on the contrary, lowered its threshold.

It may be assumed that lack of natural ventilator response to an oxygen-poor media would lead to an intensified hypoxemic shift, and thereby to an increase of corresponding hemoreceptor pulsations. However, the cited data do not support this. In a fixed respiration regime, the decrease in oxygen saturation of the blood was not more, but even somewhat less, than under free breathing conditions. Thus, in a 15-minute respiration of a mixture containing 12% O_2, the decrease in oxygenation of the blood during a free regime was 5.5 ± 1.9% more than in the very same people during a fixed breathing regime.

This fact might seem strange, as ventilator response had to compensate exactly for the decreased oxygen entering the alveoli. But it must be taken into account that increased ventilation is not always accompanied by an adequate increase of pulmonary blood flow. This disparity between perfusion and ventilation lowers the efficiency of pulmonary gaseous exchange (Dirken and Heemstra, 1947-1948, et al). Another reason for the comparatively high oxygenation of the blood during fixed breathing of hypoxic mixtures could be the lowered utilization of oxygen by the tissues. In fact, under these conditions oxygen consumption is considerably less than in free breathing. For example, at the 15th minute of freely breathing a mixture with 12% O_2, the difference was 70 ± 27 ml O_2/min. Possibly, the slowing down of the oxidizing processes in an organism during a fixed level of ventilation occurred because of the

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conditioned reflex connections between the metabolism level and respiration. Or it might have been caused by the presence in the central nervous system of a strong dominant center directed at suppressing the ventilator response to hypoxia.

Analyzing the distinction of hypoxic mixtures during free breathing (see page 64), we made the assumption that part of the unpleasant sensations of man might be connected with hypocapnia as one of the effects of increased ventilation. Under these conditions of a constant ventilation regime, this factor completely disappears. As our data showed, in breathing hypoxic mixtures alveolar P_{CO_2} hardly changes at all.

We assume that the basic reason for increased negative response to mixtures <u>/77</u> with lowered oxygen content in a fixed respiratory regime lies in the conflict between the hypoxic stimulus from an internal medium (stimulus of the respiratory response) and the slowing process issuing from the cortex of the brain. This is illustrated by the verbal reports of the subjects. Besides the usual "hard to breathe" statements, they often stated: "not enough air", "I want to inhale deeper", etc.

When the hypoxic stimulation reached a specific strength, such a conflict was solved by ventilator response. Involuntary intensification (more sharp increase of frequency) of respiration began. Similar cutoffs often occurred in inhaling mixtures containing 12 - 9% O_2, and took place in the majority of subjects when the oxygen concentration in a respiratory mixture was lowered to 7% (Figure 27).

In Chapter II it was shown that inhaling oxygen does not change the volume of ventilation much. Evidently, in connection with this fact, response to pure oxygen in a fixed regime differs little from the response observed under free breathing conditions.

A

% H in O_2 $9\%O_2$ in N_2 $21\%O_2$ in N_2 $9\%O_2$ in N_2 $21\%O_2$ in N_2 $9\%O_2$ in N_2 $21\%O_2$ in N_2

3 72 84 8̈ 8f 90 87 84 87 81 78 84 87 8̈ 78 78 81 8f 93 8f 3f 8f 8f 78 37 8̈ beats/min.
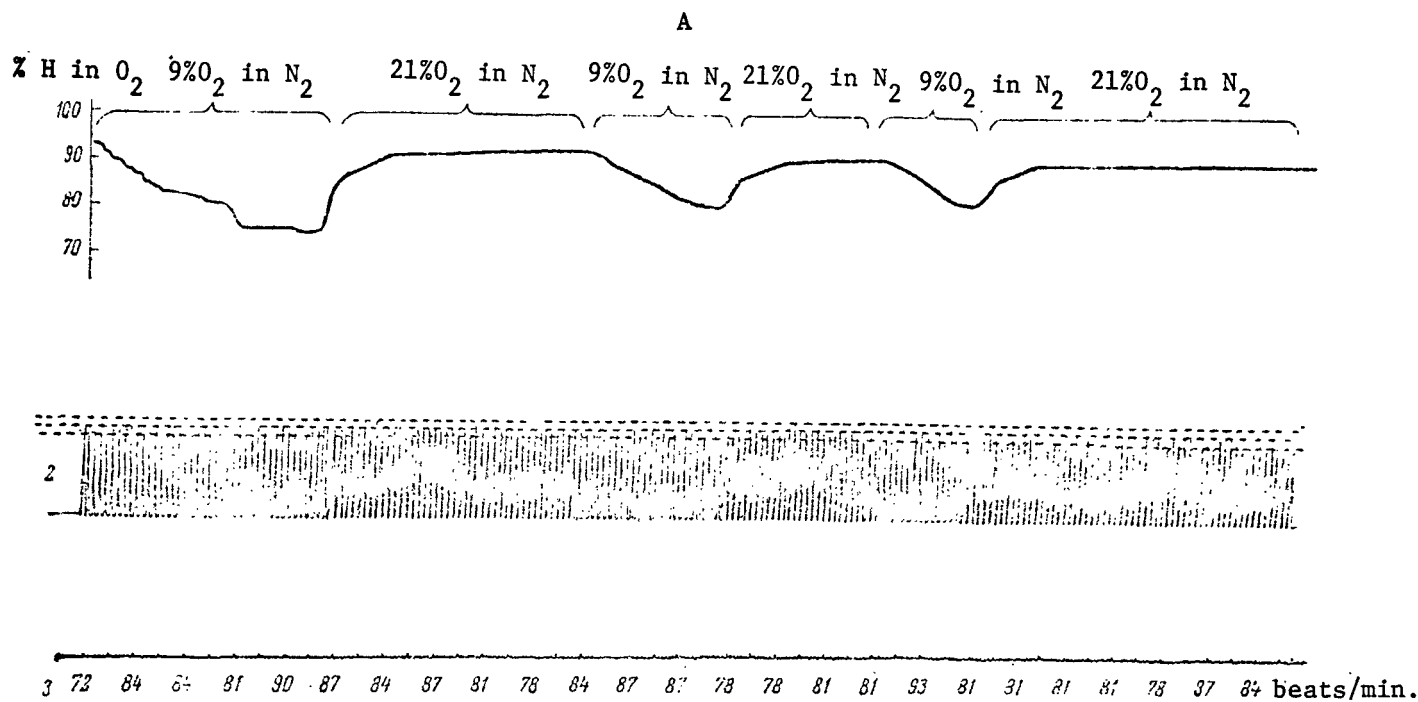
Figure 27. Spirogram and oxygen saturation of the blood in man under conditions of a fixed respiration regime with inhalation of air and hypoxic mixtures. A - respiration of a mixture with 9% O_2 content, given parameters are maintained, the air mixture is preferred to the hypoxic; B - respiration of a mixture with 7% O_2 content, a cutoff of a given volume begins, negative response to an hypoxic mixture is still more evident. Shaded line - minimum, average, and maximum respiratory volumes. The rest of the legend is the same as in Figure 8.

Figure 27 (Continued)

HYPERCAPNIC GAS PREFERENCE

If, under ordinary conditions as shown in Chapter II, the threshold of man's ability to distinguish hypercapnic mixtures in 5-minute exposures is revealed in the interval between 3 and 4% CO_2, then in a fixed breathing regime, mixtures with even 1-2% CO_2 content would often be rejected by the subjects. But a negative choice response to more concentrated hypercapnic mixtures appears much more clearly than in free breathing (Figure 28).

Obviously, man's increased ability to distinguish these media under fixed respiratory regime conditions is due to the known difficulty of arbitrarily suppressing ventilator response to excess carbon dioxide.

Even in inhaling mixtures containing 1% CO_2, frequent cutoffs of a given volume of respiration are observed. With the CO_2 content in mixtures of 4-5%, many subjects could endure neither the depth nor the rhythm of the respiratory movements demanded by the instructions. With increased carbon dioxide concentration, impairment of the fixed respiratory regime became all the more frequent.

Hypercapnic shifts were expressed more strongly under these conditions than in free breathing of the same mixtures. Inhalation of mixtures containing only 2% CO_2 increased the alveolar pressure of this gas to 6 mm Hg.

Evidently, a similar carbon dioxide excess in the internal medium, coupled with the difficulty of repressing respiratory responses to this lack, is also a reason why negative preference in inhaling a hypercapnic mixtures not only does not weaken, but even intensifies, under fixed ventilation conditions. The re-   /80 moval of one of the factors of negative responses to hypercapnia (increased load on the respiratory muscles during hyperventilation) was followed by the introduction of a new negative factor.

In one of the series of experiments, the "tuning" of the subjects' breathing was changed. At first, in the control experiment, they freely breathed

a mixture containing 3% CO_2 and 21% O_2 in nitrogen. The depth and frequency of respiration observed then were recorded. The subjects had to observe this same increased respiratory regime in the following experiments.

Under conditions of such a fixed hyperventilation when the subjects were offered ordinary air and a mixture containing 3% CO_2, the overwhelming majority chose the latter (Figure 29).
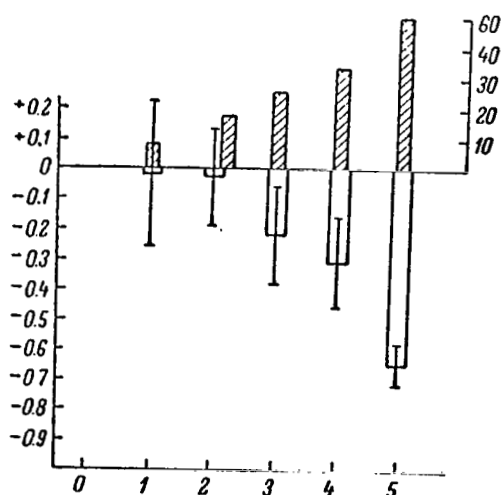
Figure 28. Hypercapnic gas preference of man under conditions of a fixed respiration regime. Average data from 12 subjects. Shaded columns – number of "cutoffs" of a given respiratory volume (in % of the number of experiments). The rest of the legend is the same as in Figures 7 and 14.
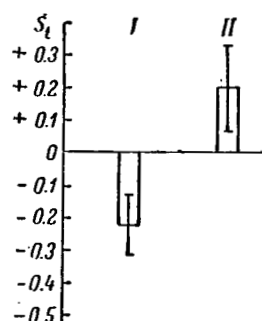
Figure 29. Hypercapnic gas preference in man under conditions of a fixed respiration regime "tuned" to an air (I) and to a hypercapnic (II) mixture. Average data from 12 subjects. Vertically – choice index of a mixture with 3% CO_2 content (S_t).

It is clear that if, at an ordinary level of ventilation, a man exhibits a negative response to this mixture, avoiding hypercapnia, then in an experiment thus arranged he avoids, on the other hand, hypocapnia, developing with the increased ventilation of air. In this case, the mixture containing excess carbon dioxide eliminated hypocapnia; therefore, evidently, it was also preferred by the subjects.

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Here the interrelationship of chemical and reflex respiratory responses might also play a definite role. There is evidence that dilation of the lungs by the Hering*-Brerer reflexes lowers the sensitivity of the respiratory center to carbon dioxide (Fowler, 1954; Opie, et al., 1959). Therefore, increased respiration depth, because of the inhibiting influence of pulmonary mechanoreceptor excitation (negative feedback), decreases the "conscious perception of chemical stimulus". It allows a man to maintain a given respiratory volume when there is a large carbon dioxide concentration in an inhaled mixture (Remmers, et al., 1968).

HYPOXIC-HYPERCAPNIC GAS PREFERENCE

Let us discuss how man reacted under fixed respiratory regime conditions to hypoxic mixtures on a background of a hypercapnic mixture (3% CO_2 in the undifferentiated and in the differentiated mixtures).

Two versions of the experiments were conducted. In the first version the subjects breathed, and the ordinary parameters were observed (rhythm and respiration volume) which were established for them in air breathing (Figure 30, A). Under these conditions the "undifferentiated" mixture (3% CO_2 + 21% O_2) was not in the strict sense indifferent, as it caused hypercapnic shifts in man.

Regarding this choice response, the mixtures here containing 18 and 15% O_2 were not distinguished by the subjects from normally oxygenated mixtures in 5-minute respiration. Many people under these conditions could not even endure the given volume of respiration. A 12% mixture even caused certain negative responses accompanied by complaints about the sharp worsening of general feeling (dizziness, sweating). Cases of given respiration parameters being cut off were more frequent. These effects were expressed still more stongly in breathing a hypercapnic mixture containing 9% O_2.

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*Translator's Note: This is named after Ewald Hering, a German physiologist.
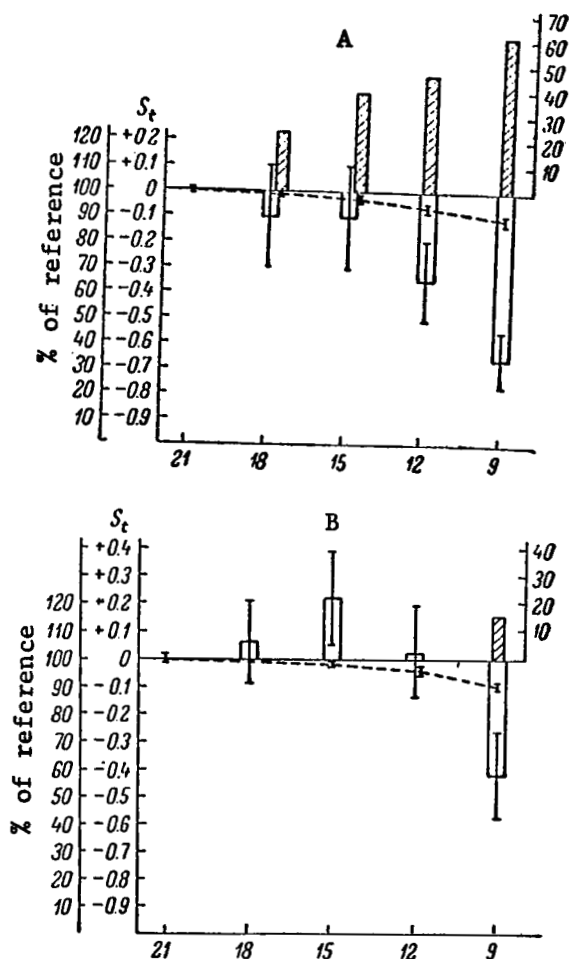
Figure 30. Hypoxic gas preference of man in a medium of added carbon dioxide (3%) under conditions of a fixed respiration regime "tuned" to air (A) and to a mixture with 3% CO_2 (B). The rest of the legend is the same as in Figures 7 and 26.

Thus, in this case also, repression of ventilator response improved the conditions of man's distinguishing hypercapnic media.

In the second version of the experiments, the regime of the subjects was "tuned" to a normal oxygen mixture containing 3% CO_2, as was described on page 85. Consequently, here the undifferentiated mixture (3% CO_2 + 21% O_2) was completely adequate for the subjects' ventilation.

It is natural that in connection with increased VRM in these experiments hypoxic mixtures caused less lowering of oxygenation of the blood and increased pulse frequency than in the respiration "tuned" to air (Figure 30, B).

At the same time a considerable /83 portion of the subjects displayed a positive response in relation to mixtures containing 18-12% O_2, and avoided breathing the undifferentiated mixture. This paradoxical effect is not difficult to explain as the mixtures with a somewhat lowered oxygen content were more adequate for the increased level of ventilation. It could also affect the mentioned inhibiting influence of the lowered respiratory volume on the chemical sensitivity of the respiration regulation apparatus. Only a 9% mixture caused a definite negative response in the subjects. Disruption of the given respiratory regime occurred here.

* * *

Therefore, under fixed respiration regime conditions, man's ability to distinguish changes of the gas composition of inhaled mixtures is stronger than under ordinary conditions. Man clearly selects those media whose content is more adequate for a given volume of pulmonary ventilation and responds negatively to mixtures whose respiration in a given regime involves impairment of the gas content of the internal medium — hypoxia, hypercapnia, or hypocapnia.

This shows that gas preference responses to mixtures with altered oxygen and carbon dioxide content are not basically determined by the load on the respiratory muscles. Otherwise, the ability of man to distinguish gas mixtures in fixed respiration regime conditions would not increase, but on the contrary, disappear because of ventilator response to this mixture. If the energy factor also plays some kind of a role here, then it is only a secondary one[1]. The organism responds mostly to hypoxic and hypercapnic shifts in the internal medium. When we, with the help of arbitrary stress, hinder the reflex apparatus of an adequate ventilation level in response to these shifts, negative choice, and consequently, also distinction of corresponding mixtures increases. This evidently occurs because of a conflict between the stimulating and inhibiting processes in the cortex of the brain which coordinate respiration with other functions (Kocherga, 1966).

The question of man's ability to maintain a constant regime of respiratory movement also is of independent importance. There is information that this ability remains in moderate hypoxia, in an "ascent" in an altitude chamber to an altitude of 5 km (Buteyko, et al, 1966). But if the oxygen content in the   /84
medium is significantly lowered (according to our data below 9%), arbitrary regulation of respiration still cannot retard hypoxic stimulation, even in a short length of time. Regulatory mechanisms are even more sensitive to hypercapnia. Just a 3% CO_2 content in the inhaled mixture causes disturbance of a given respiration regime in some people. However, man's strongest ability to activate ventilation response arbitrarily is impaired when a shortage of oxygen

[1] This does not pertain to breathing helium mixtures. Due to the significant difference between the physical properties of respiratory media, the energy factor is of decisive importance in gas preference responses (see Chapter III).

in the respiratory medium is combined with excess carbon dioxide, i.e., under the influence of the most adequate stimulator of respiration, active in muscle work. According to the observations of Y.I. Dan'ko (1964, 1967) in intense muscular activity man does not seem to be in a position to regulate his respiration arbitrarily.

Man's gas preference response, on one hand, and the ability to direct his respiration, on the other, have a common element — a verbal self-report, which is also a most important component of any arbitrary (conscious) activity.

The research of K.M. Smirnov, et al., 1962, 1964, 1966, showed that in fulfilling the instructions about changing depth or rhythm of his breathing a man necessarily repeats the task to himself.

The perception of one or other afferent impulses, caused by a change in the composition of a respiratory medium, must also evidently reach a level at which it can be verbalized to cause an arbitrary act of choosing a mixture. According to information from our subjects, in evaluating the respiratory mixtures offered to them during the experiment, they necessarily spoke to themselves ("the right mixture is kind of stifling", "the left one was easier to breathe", "this mixture should be ended quicker, I can't breathe it any more", etc.). It was indicated in Chapter I that discrepancies between verbal report and actual choice of gas mixtures were quite rare.

As will be shown, in the process of training man to distinguish gas media, this generality of gas preference responses with arbitrary respiration regulation is clearly revealed.

Chapter V

RECEPTORS FOR RESPONSES TO THE ALTERED GAS MEDIUM

Which specific receptors emit the information on the gas composition of
the external and internal media, which provides for an adequate body reaction
to varying compositions of respiratory mixtures?

Unfortunately, Soviet literature does not include a single state-of-the-
art work in this field. Hence, it was felt that this problem should be discussed
in some detail.

MECHANISMS FOR THE PERCEPTION OF THE GAS ENVIRONMENT COMPOSITION

We will now consider the receptor, which can be included in the "gas
analyzer" of the given organism, based on data that were obtained as a result
of intensive studies, conducted in recent years in the field of respiratory con-
trol and chemoreception.

Chemoreceptors of the Respiratory Tract and Lungs

It is logical to assume that the composition of the respiratory gas media
is perceived at the "intake" into the organism, similar to food. This accounts
for numerous attempts, made by investigators, to discover the appropriate sens-
ors. In fact, the inspired air first of all makes contact with the mucosa of
the upper respiratory tract, which serves as a receptor field for the reactions
to miscellaneous irritants, including chemical irritants. Could it just be that
these receptors control the composition of the inspired air?

Ye.N. Pavlovskiy (1937) noted the sensitivity of nasal mucosa to increased CO_2 concentration; this sensitivity decreased after neurotomy of the trigeminal nerve (fifth cranial nerve). V.A. Bukov (1941) passed gaseous mixtures separately through the larynx and through the upper respiratory tracts. He was able to observe respiratory and blood circulation reactions, which could be correlated with the CO_2 content in the gas mixtures used; after cocainization of the mucosa, /8(these reactions disappeared.

However, these findings were not confirmed in subsequent studies; thus, the presence of chemoreceptors participating in breathing control in the respiratory tracts of mammals cannot be considered an established fact. The aforementioned studies by Ye.N. Pavlovskiy and V.A. Bukov conceivably might have dealt with artefacts, if we consider the sensitivity of the mucosa of the upper respiratory tract to the mechanical action of airflow (Lopatina, 1948); Fel'berbaum, 1963; Sagalovich, 1967; Comroe, 1967, and others.

The remarkable constancy of alveolar air composition led many physiologists to assume the existence of receptors which control the pressure of gases in alveolae, or in the blood from the lungs.

In pulmonary alveolae, morphologists were discovering certain special cluster-like or dendritic nerve endings. Assumptions were made that these nerve endings may be the ones that perceive the variation of the composition of the alveolar air (Larsell, 1922; Partridge, 1944, Lashkov, 1963).

Back in the 19th century, Traube (1847, cited from Cordier and Heymans, 1935) thought that chemical irritations are transmitted directly to the respiratory center from the lungs. Notably, pulmonary irritation by toxic agents causes dyspnea (Mayer, 1925, cited from Cordier and Heymans, 1935, and many others). Ammonia vapors cause a reflectory stoppage of breathing (Dauterband, 1933; Vinokurov, 1948, et al). In addition, data were obtained, supporting the contention regarding the effect of CO_2 upon pulmonary receptors. Pi-Suñer and Bellido, 1921 (cited from Cordier and Heymans, 1935) ventilating lungs perfused by CO_2-rich mixtures (greater than 20%), noted a reflex

excitation of the respiratory center of an isolated animal head over the vagus nerve (tenth cranial nerve). Some investigators concluded that lungs contain receptors, reacting to the CO_2 of the inspired air (Pi-Suñer, 1947). Hortolomeri, et al., 1963, introduced oxygen through a probe, inserted into the main bronchus, and observed a decrease of the amplitude and of the breathing rate; opposite effects took place with CO_2 mixtures.

In spite of these investigations, most authors do not attribute a substantial role in breathing control to pulmonary chemoreceptors (Heymans and Heymans, 1927; Dejours, 1962, et al.). Following is the basis for this viewpoint:

(1)   The ventilation of isolated lungs, connected to an isolated head only by means of pneumogastric nerves, using hypoxic or hypercarpic mixtures, does not affect the function of the respiratory   /87 center; Pi-Suñer's findings can be attributed to the application of obviously non-physiological concentrations of CO_2 (Heymands and Heymans, 1927).

(2)   The inspiration of mixtures, containing 10% CO_2, does not cause an increased impulse rate in the afferent fiber of the pulmonary branches of pneumogastric nerves (Keller and Loeser, 1930; Partridge, 1933).

(3)   During the inspiration of CO_2-enriched mixtures, increased ventilation lags behind the shift of alveolar pressure of CO_2; apparently it sets in only when the increased CO_2 pressure of the blood begins to affect the arterial chemoreceptors and the respiratory center (Read, et al., 1964).

Cordier and Heymans (1935) stipulated that the alveolar content of CO_2, within physiological or even within pathophysiological limits, has no reflex influence upon the respiratory center, and that the sensitive endings of the vagus nerve in the lungs can be stimulated only by powerful chemical irritants. The stimulation of these receptors, during the variation of the composition of

the inspired air can, without doubt, induce only local reflexes, affecting the control of the bronchial lumen (Nissel, 1950), and the pulmonary vessels (Dirken Heemstra, 1947-48; Cook, et al., 1963).

It will be demonstrated in the following that, according to current data, there are apparently no receptors for the gas composition of the blood in the vessels of the pulmonary circulatory system. Instead, the crucial role in the control of the internal gas media of the organism belongs to the chemoreceptors of the Willis circle[*], i.e., sinocarotid and aortic.

Aortic and Sinocarotid Chemoreceptors

In the 20th Century, J.F. Heymans and C. Heymans demonstrated the existence of special sensing elements, adapted for the perception of variations of the chemical composition of the blood. Along with baroreceptors, which regulate the blood pressure and were discovered by Ludwig, Zion, and Gehring, these sensing elements are located in the wall of the arcus aortae, as well as at the external/internal bifurcation of the carotid artery.

A perfusion of the cardiac-aortic region by acapnic or hypercapnic blood produced an inhibition or stimulation of the respiratory center, respectively (Heymans and Heymans, 1927). A similar response of the carotid sinus zone turned out to be even more significant (Heymans and Bouckaert, 1930). It was found that when a donor dog, during a perfusion of the vasoisolated carotid sinus, inspires mixtures containing 5 to 10% CO_2, the recipient dog displays an acute reflex respiratory stimulation. The same effect was observed when the /88 donor dog was breathing nitrogen or hydrogen. Denervation of the aortic or sinocarotid zones considerably reduced or completely eliminated the hypoxic reaction: some animals died from hyposidosis without any reaction from the respiratory center, others displayed (dyspnea) only at extreme stages of hypoxia (Heymans, et al., 1932). Thus, it was established that afferent nerve

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[*]Translator's Note: This is circulus arteriosis cerebri.

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endings in sinocarotids are stimulated by oxygen insufficiency and excess of carbonic acid in the circulating blood.

The carotid body (as well as the aortic body) is a nodule (glomus) consisting of chromaffine tissue and containing cavities which receive the blood from the thin branch of the carotid artery. Under the endothelium of these cavities are numerous nerve endings which receive the chemical stimuli (DeCastro, 1928, cited from Cordier and Heymans, 1935). The afferent fibers of sinocarotid receptors form the sinus nerve, or Hering nerve, which is a branch of the IXth pair (ramus caroticus n. glossopharyngei, s. sinusvernus; Hering, 1923). The aortic body emits afferent fibers within the aortic branch of the pneumogastric nerve (ramus aorticus n. vagi).

Phylogenesis and Ontogenesis. Chemoreceptors that are homologous to the carotid receptors were discovered in the area of branchial vessels of fishes and amphibial larvae (Kravchinskiy, 1945). There are numerous indications supporting the contention that the origin of the receptors of the carotid and of the aortic glomera of higher animals is related to the evolution of ganglious tissue in the area of branchial vessesls (Koch, 1931; Boyd, 1937, cited from Kravchinskiy, 1945; Bystrov, 1939, cited from Chernigovskiy, 1947; Chernigovskiy, 1947, 1960; Vinnikov, 1958). The structure and function of the glomera in reptiles, birds, and mammals are approximately the same (Heymans, 1958). Man does not represent an exception, neither with respect to the histological structure (Seto, 1935) nor with respect to the physiological role of these formations. The latter was demonstrated on patients who underwent neck surgery (Carlsten et al., 1958).

Apparently, synocarotid chemoreceptors become activated at the fetal stage. Cross and Malcolm (1952) reported on gestating sheep who were transferred to oxygen breathing after a period of hypoxia. At this moment, the activity of the sinus nerve (sinusnervus) in the fetus temporarily disappeared. Carbonic acid pressure and hydrogen ion concentration in the umbilical venous blood, between the moment of birth and the first inspiration (i.e., for 30 to 90 minutes) were drastically increased; the oxygen pressure was reduced. In view of this,

the chemoreceptive impulsation is important as a stimulator of the first respiratory motions at birth (Avery, et al., 1965; Harned, et al., 1967). In fact, there exist reports on the low activity of chemoreceptors (Miller and Smull, 1955), or else on the reduced sensitivity of the respiratorial center toward glomerogenic impulses in infants. However, other authors (Davis and Mott, 1958) found that arterial chemoreceptors in infants were functioning normally. Cross and Oppé (1952) reported an increased of VRM in children after one minute of breathing a mixture with a 15% O_2 content; subsequent inspiration of pure oxygen resulted in a rapid drop of ventilation. These reactions were even more pronounced in children than in adults, and undoubtedly account for a full-scale functioning of the chemoreceptor apparatus already at early postnatal stage.

The Function of Chemoreceptors at Normal Oxygen Pressure in the Blood. Comroe and Schmidt (1938) had previously assumed that the chemoreceptors of the arterial system under normoxy cannot play any role whatsoever in respiratory regulation, inasmuch as their excitation threshold by hypoxic blood corresponded to a P_{O_2} below 50 mm Hg.

However, in the opinion of most investigators (Heymans, et al., 1932; Gesell, 1939; Bernthal, 1944; and others), arterial chemoreceptors already become active at normal P_{O_2}. It was reported that the impulses in the sinus nerve of a cat become noticeable when the P_{O_2} pressure in arterial blood reaches 80 to 100 mm Hg (Euler, et al., 1939; Hornbein, et al., 1961. Dejours, et al., 1958), stipulated a chemoreceptor's stimulation threshold as 170 mm Hg with reference to arterial P_{O_2}. This is equivalent to a 33% oxygen content in the inspired air.

Understandably, if the blood's P_{O_2} is above the stimulation threshold of chemoreceptors, their activity must disappear. This assumption proved to be correct. When animals inspire hyperoxic mixtures, the electrical activity of the carotid body goes down (Landgrem and Zotterman, 1951). Oxygen inspiration causes a transient decrease of pulmonary ventilation in animals and in man. After the denervation of aortic and carotid reflexogenic zones, this

reaction is absent (Dripps and Comroe, 1947; Vayksleyger, et al., 1963; Dejours, 1963). Thus in the terminology used by Dripps and Comroe, oxygen produces a "physiological denervation" of the chemoreceptors.

From the aforementioned facts, it appears that at normal P_{O_2} levels the arterial chemoreceptors are in a state of tonic stimulation which is one of the factors supporting the performance of the respiratory center on a certain level.

The Role of Arterial Chemoreceptors in Hypoxic Reactions. Of utmost importance is the reaction of aortic and sinocarotid chemoreceptors in the adaptation of the organism to oxygen insufficiency. While the inspiration of hypoxic mixtures under normal conditions causes an increase of ventilation,   /90 depression of respiratory activity was observed during the first minutes of inspiration of such mixtures in animals with a chronic denervation of chemoreceptors (Wett, et al., 1934; Chambers, et al., 1947; Swieler, 1967; and others). This is naturally accompanied by a considerable decrease of the blood oxygenation (Grant, 1951; Beller, 1958).

The role of carotid glomera, as necessary sensors of oxygen insufficiency, was explicitly demonstrated in experiments by Fitzgerald, et al. (1964). The sinocarotid zone of a dog was isolated from general circulation and perfused with blood with high oxygen pressure (over 500 mm Hg) and low P_{O_2} (less than 10 mm Hg). The breathing of a hypoxic mixture produced a reduction of the pulmonary ventilation in the animal, rather than the normally expected increase.

Upon a chronic denervation of the sinocarotid chemoreceptors and a block of n. vagus, the inspiration of a 10% O_2 mixture does not appear to cause a constriction of the respiratory tract, which is typical for hypoxia (Nadel and Widdicombe, 1962). Generally, chemoreceptor reflexes provide for an increase of VRM while the oxygen content in the inspired air is decreased to about 16%. This mechanism is quite stable; in fact, it is retained even under deep sedation (Comroe, et al., 1956). The sensitivity of the arterial chemoreceptors also accounts for the ventilatory reaction of hypoxia during

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muscular activity (Hornbein and Roos, 1962).

This is the mechanism that supports the P_{O_2} level in blood; a reduction of this level is an adequate stimulant of sinocarotid and aortic chemoreceptors. In the opinion of a number of investigators, the oxygen supply of a richly-vascularized tissue indeed suffers when the P_{O_2} level of the blood is reduced. At the same time, arterial chemoreceptors are almost insensitive to the absolute content of blood oxygen which essentially is the governing factor of gas exchange in all peripheral tissues and organs. This is apparent from experiments involving loss of blood or from experiments involving the inspiration of a mixture that, as known, reduces the percentage or oxyghemoglobin in blood. With such hemic hypoxia, the ventilatory reactions as well as an increase of the sinocarotid chemoreceptoral activity of the experimental animal are either weakly pronounced, or totally absent (Comroe and Schmidt, 1938; Ardashikova and Shik, 1948; Duke et al., 1952; Horner, 1965).

In all instances of oxyen insufficiency in the media and a decrease of oxygen pressure in blood, the reflexes of arterial chemoreceptors emerge as the most important mechanism of adequate reations of the respiratory system (Ardashnikova, 1959, 1966).

The Sensitivity of Arterial Chemoreceptors to Carbonic Acid. Do aortal and carotide chemoreceptors react to the carbonic acid level in the blood?

Haldane and Smith (1893, cited from Haldane and Priestley, 1935) found no relationship between the influence of vagotomy upon the onset time of hyperpnoea in rabbits, who were breathing a mixture with a 20% concentration of CO_2. Gemill and Reeves (1933) reported that the respiratory response of dogs to variations of carbon dioxide content in the inspired air did not change after denervation, or after the removal of the carotid body. It would therefore appear that, under normal conditions, a stimulation of the chemoreceptors of the arterial tract by carbonic acid should not participate in breathing regulation. On the basis of these facts, Comroe (1939) assumed that chemoreceptors become

involved only at extreme stages of hypercapnia.

Some findings indicate that at the same time a variation of the P_{CO_2} of the blood, that perfuses the carotid body, produces an almost instantaneous change of the electrical activity of the chemoreceptors; this change takes place without any noticeable adaptation (Saaman and Stella, 1935). Moreover, it was established that carbonic acid stimulates the chemoreceptors under normocapnic conditions (Gesell, et al., 1940; Euler and Lilejestrand, 1940-41). Apparently, the sensitivity threshold for arterial chemoreceptors is equivalent to a P_{CO_2} of about 20 to 30 mm Hg, i.e., it is somewhat below the normal P_{CO_2} of blood. An increase of carbonic acid pressure above this level is followed by a linear increase of the afferentia from the carotid sinus (Bartels and Witzleb, 1956; Krylov, 1966).

The initial ventilation increase in cats, caused by the inspiration of a hypercapnic mixture, takes place parallel to the amplification of the impulsation in afferent fibers that innervate the carotid glomus (Leitner, et al., 1965). The inspiration of 1-2 volumes of 6% CO_2 mixtures (CO_2 test) increases the pulmonary ventilation in dogs and cats after 5-10 seconds; another 5 seconds later the ventilatory response reaches its maximum (130% compared to the initial ventilation). After denervation of the sinocarotid zone, this early hyperpnoea is not observed. VRM increases sluggishly and late (more than after 15 seconds), on account of the central action of the carbonic acid (Bouverot, et al., 1961, 1963, 1965; Dejours, 1963; Colard, et al., 1965; Florez and Borison, 1967).

Consequently, the arterial chemoreceptive mechanism also participates in sustaining the constancy of P_{CO_2} in the blood. This mechanism is particularly important in reactions involving rapid changes of P_{CO_2} in the blood (Dutton, et al., 1967). However, when P_{O_2} in arterial blood is sufficiently high, the isolated effect of carbonic acid and hydrogen ions upon the chemoreceptors of the carotid region is apparently insignificant, when compared to

the central influences (Katsaros and Loeschke, 1964; Katsaros, 1965).

Some recent discussions involved the rhythmic oscillations of P_{CO_2} and P_{O_2} in blood that are related to the respiratory cycle. Several authors attributed to these oscillations an important role in the reflex stimulation of arguing that arterial chemoreceptors are considerably more sensitive to intermittent than to constant stimulation. However, some recently published studies demonstrate that ventilation is maintained on a level which is equivalent to the average alveolar P_{CO_2} and P_{O_2}, regardless of the variation of these quantities between inspiration and expiration (Cunningham, et al., 1965).

The Physiological Mechanism of Arterial Chemoreflexes. It was demonstrated that aortic and carotid chemoreceptors react above all to oxygen insufficiency in the circulating blood. A very considerable quantity of blood circulates through the vessels of the glomus tissue (2 liters/minute/100 grams of tissue); hence the venous P_{O_2} here is close to the arterial. At the same time, the carotid body has a very low oxygen consumption, i.e., 9 ml/minute/100 grams of tissue (Daly, et al., 1954). It was assumed that chemoreceptor stimulation, related to oxygen insufficiency, is caused by the imbalance of the oxygenation metabolism of the glomus tissue, possibly produced by a natural transmitter — acetylcholine[*] (Joels and Neil, 1962).

A local oxygen insufficiency may be caused not just by the decrease of its pressure in the blood, but also by a decrease of the blood supply to the glomera. In fact, there is an acute gain in electrical activity of the chemoreceptor fibers when the blood flow in the carotid sinus is reduced (Floyd and Heil, 1952; Neil, 1961), and when arterial blood pressure is lowered (Bjursted and Hesser, 1942, et al.). Chemoreceptors also become more active when the temperature of the circulating blood goes up (Bernthal and Weeks, 1939; Witzleb, 1952; Eyzaguirre and Lewin, 1961); this can be explained by the increased

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[*]Translator's note: Acetylcholine structural formula is
$$CH_3 \cdot CO \cdot O \cdot C_2H_4 \cdot N(CH_3)_3OH$$
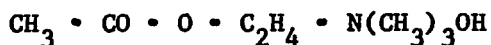
oxygen requirement of the glomus tissue.

We saw that arterial chemoreceptors are also stimulated by carbonic acid. In this respect, the relationship between carbonic acid and hydrogen ion concentration of the blood (Zotterman, 1935; and others) is of great significance, even though some authors hold that P_{CO_2} and C_H stimulate the chemoreceptors independently of each other (Joels and Neil, 1960; Lebedeva, 1965). In any event, oxygen insufficiency and hydrocarbonic acid excess are positively interacting stimuli for chemoreceptors. This will be discussed in some detail hereafter.

Most investigators feel that there exist specialized nerve endings that are sensitive either to an excess of carbonic acid and hydrogen ions, or to oxygen insufficiency (Winter, 1942; and others). This contention is supported by the stimulation of different afferent fibers, depending on which of the agents is acting upon the receptors (Heymans and Neil, 1958). It also is assumed that there are two types of chemoreceptors: some are stimulated by the acidity of the media and by acetylcholine under extreme conditions, whereas others are /93 stimulated by oxygen insufficiency, i.e., a threat to the energy balance of the tissues (Krylov, 1963). There is also a school of thought that holds that the receptors are of a uniform nature, and react upon oxygen insufficiency as well as upon shifts of P_{CO_2} and the pH of tissue (Joels and Neil, 1962). Thus, Eyzaguirre and Koyano (1965) observed the activation of the chemoreceptors of the carotid body of a cat *in vitro* by oxygen insufficiency, by excess of carbonic acid and by the acidity of the media, as well as by a decreased current of the circulating solution. Analysis of the biocurrents of a single chemoreceptor fiber indicates that the overwhelming majority of such fibers are activated by any form of stimulant. The authors hold that an adequate stimulation causes, in turn, a release of specific agents from the glomus cell; these cells, in turn, stimulate a trigger reaction of the sensory fiber which takes place according to the law "all or nothing".

It is quite conceivable that the same finite link participates in the stimulation mechanism of chemoreceptors, regardless of the factors that cause the stimulation. A common factor in the reaction to a variety of chemical

stimulants is the depolarization of receptor terminals. V.A. Lebedeva (1965) reached this conclusion upon analyzing experimental data regarding a complex problem on the nature of chemical sensitivity in general and the reception of carbonic acid in particular; incidentally, this problem is still far from being solved. V.N. Chernigovskiy (1947, 1960) holds that agents such as oxygen insufficiency, excess of carbonic acid, hydrogen ion concentration, and cyanides act upon chemoreceptors by changing the metabolism of the tissue cells. This is supported by experiments, involving the blocking of receptors by sodium fluoride or monoiodoacetic acid; morphological data also appear to support this contention. As opposed to pressoreceptive endings, the chemoreceptive ending (including those in the carotid sinuses) are not located in the vascular wall, but in the cells of the corresponding parts (Lavrent'yev, 1943).

Extremely important are the data by M.L. Belen'kiy who demonstrated that chemoreceptive cells are stimulated when the catabolism of a macroerg of ATP[*] in the tissue of a carotid glomus predominates over its resynthesis. In the light of these findings, impulsation from the glomera acts like a signal warning about the danger of overconsumption of the energy resources of the tissues (Belen'kiy, 1952; Anichkov and Belen'kiy, 1962).

Such is the important and varied role of aortic and particularly sinocarotid chemoreceptors. It is hardly surprising that elimination of these receptors (removal, denervation, cold block) not only deprives the organism of the capability to regulate blood and tissue oxygenation, including that of the brain, with sufficient responsiveness (Beller, 1958; Grechishkin, 1964; Krylov, 1966), but also reduces pulmonary ventilation and brings about a general depression of the physiological functions (Gessel, et al., 1940; Belen'kiy, 1952).   /94

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[*]Translator's Note: adenosin - e triphosphate.

Chemoreceptors of Peripheral Vessels, Tissues, and of the Venous Channel

Are there devices that record the pressure of oxygen and of carbonic acid in other areas of the vascular system (outside of the aortic and sinocarotid), as well as in body tissues?

Inasmuch as the composition of mixed venous blood to a certain extent depends on the energy metabolism of the organism, Zuntz and Heppert (1886) in the 19th century suggested the existence of special receptors in the right heart and in the pulmonary artery which regulate the functions of respiratory and vasomotor centers. Subsequently, a hypothesis was advanced suggesting the existence of so-called "metaboreceptors" which perceive the contents of metabolic products in the blood and participate in respiratory regulation. This was apparently supported by experiments with cross-blood circulation in dogs and by the introduction of 2,4-dinitrophenol into the isolated rear extremity of the "neural" animal which produced an increase of ventilation in both animals (Ramsay, 1959). Indeed, when the neural bonds between the working extremity and the respiratory center are disrupted, the ventilatory response to muscular activity decreases (Kao et al., 1963). Some investigators pointed out that when man is transferred to breathing a hypercapnic mixture, the complete ventilatory reaction is delayed by two minutes as compared to an increase of the alveolar P_{CO_2}. This was explained by the fact that the respiratory response is predicted on a gradual increase of P_{CO_2}, particularly in mixed venous blood. An important argument in favor of the existence of venous chemoreceptors is the exact proportionality between the ventilation levels and venous P_{CO_2}, when blood is artificially enriched by carbonic acid, as well as during moderate muscular activity (Yamamoto and Edwards, 1960). No such relationship was observed between ventilation and arterial P_{CO_2}. Using this mechanism, some authors attempted to explain certain questionable elements in respiratory regulation, particularly during muscular activity (Dutton et al., 1960; Riley et al., 1961). Glomus islet-cell tissue, comparable to corresponding formations of aortic and sinocarotid zones, was discovered in veins (Krage, 1962). Similar islets were discovered in the pulmonary artery (Heymans, 1934; Elftman, 1943;

Boyd, 1961). Again, the assumption was made that chemoreceptors in the pulmonary artery regulate the activity of the respiratory center, responding to the composition of the mixed venous blood (Armstrong et al., 1961).

However, as of now, there is no direct evidence of the existence of these chemoreceptors. Riley et al., (1963) and Paintal and Riley (1966) submit a serious argument against the existence of a direct perception of the gas compo- /95 sition of venous blood. Thus, impulses in a single chemoreceptive fiber of the aortic nerve were registered in a cat. These fibers were identified as chemoreceptors on account of increased discharges during asphyxia. Upon introducing nicotine into the right heart or into the root of the aorta, this impulsation notably increased. Judging from the latent period of this reaction, all fibers originate from the arteries of the greater circulatory system, rather than from the right heart or the pulmonary artery. Riley attempts to explain the parallelism between the ventilation and the venous P_{CO_2} by referring to the aforenamed hypothesis of respiratory regulation under the influence of the oscillations of arterial P_{CO_2} which, in turn, depend on the mixed venous P_{CO_2} (particularly during muscular activity).

The extreme significance of peripheral "metaboreceptors" in the regulation of respiratory activity has been obviously quite exaggerated. In experiments with the perfusion of a vascularly isolated extremity, asphyxia of the donor animal did not cause hyperpnoea of the "neural" animal (Comroe and Schmidt, 1943; Iaria et al., 1959), whereas the positive results obtained by Ramsay, using the same methods, were explained as a consequence of loss of blood, rather than the result of stimulation of specific chemoreceptors (Bailen and Howath, 1959). Ischemia of the extremities, where a quantity of metabolic products should have accummulated that was expected to be quite adequate for the stimulation of the hypothetic chemoreceptors, was not accompanied by any variations of breathing in man (Asmussen et al., 1943). Dejours et al., (1955) performed the following experiment: At the end of muscular legwork by man, circulation in the femoral vessels was interrupted and, after two minutes, suddenly restored. After 18 seconds, the subject showed an unexpected increase of the ventilation which was always preceded by a drop in the saturation of the arterial blood

measured by an aural oxymeter. Ischemic hypoxia of other organs has no effect upon respiration either (Ardashnikova, 1965). No effects were obtained even with the introduction of moderate concentrations of acids and alkalis into vena femoralis (Heymans et al., 1932; Schmidt and Comroe, 1940). In those instances when these agents did change respiration, the causes may have been pain stimuli or non-physiological concentrations of the introduced substances (Dejours, 1962).

At the same time, it can be assumed that local chemical shifts in working muscles increase the sensibility of mechanoreceptors which, in turn, affect respiration (Dejours et al., 1957; Bessour et al., 1959). Here, we should take into account the general property of interoreceptors to raise their irritability at certain stages of hypoxia (Pozdnyakova, 1963).

Contributions by V.N. Chernigovskiy (1947, 1960) and by his collaborators (Lebedeva, 1964, et al.), dealing with the perfusion of different internal organs, demonstrated that the peripheral vascular network has an abundance of chemoreceptors which are in many ways similar to the carotid and aortic, even though they are more sensitive to carbonic acid than to oxygen insufficiency. However, in view of the low irritiability (Stegeman and Böning, 1967), and a /96 long latent period, it would appear that these local chemoreceptors most likely play a role in the regulation of local processes only (Sergiyevskiy, 1967).

The Immediate Chemical Sensitivity of the Respiratory Center

Rosenthal (1862) was the first to demonstrate the existence of a close relationship between the activity of the respiratory center of the myelencephalon and the chemical composition (venosity) of the blood circulating through the brain. According to Geppert and Zuntz (1888), cited by Cordier and Heymans (1935), a neurotomy of the conductors between working muscles and the myelencephalon does not affect the respiratory response to muscular work. However, this response disappears if the working muscles are excluded from the general blood circulation. In Fredericq's experiments (1901), cited by Haldane and Priestley (1935), animal heads were subjected to cross-circulation; when the donor-animal was exposed to oxygen starvation, the recipient displayed dispnoea

symptoms, and even convulsions, whereas the donor was more inclined to apnoea. However, in this experiment the chemoreceptors (as yet unknown) may have played a significant role, in addition to the respiratory center.

Lindhard (1912), cited from Vayksleger and Yeremenko (1964), stipulated the inverse relationship between the sensitivity of the respiratory centers and the oxygen blood pressure. Later, however, it became apparent that carbonic acid, rather than oxygen, plays the predominant role in the chemical stimulation of the respiratory center. Bersques (1953), cited from Sergiyevskiy and Ivanov (1961), demonstrated that oxygen, dissolved in cerebrospiral fluid, has no effect upon respiratory or upon vasometric centers.

Hooker et al., (1917) cited by Cordier and Heymans (1935), perfused the myeloencephalon using defibrinized blood with the same pH, but different P_{CO_2}. He was able to establish that blood, equalized by 5% CO_2, increases pulmonary ventilation. It was assumed (Winterstein, 1921; Gesell, 1929; Cordier and Heymans, 1935) that carbonic acid has no direct influence upon the respiratory center, i.e., the work of the center is regulated in accordance with the active reaction in its cells, possibly as a result of the direct influence of hydrogen ion concentration of the blood (Hanus et al., 1944). Direct experiments (Katz et al., 1963; and others) lead us to believe that the variations of both pH and P_{CO_2} in the respiratory center do indeed affect the ventilation.

What is the specific action mechanism of these chemical factors, as it affects the work of respiratory centers? According to Haldane and Priestley (1935), the chemical influences upon the respiratory centers define the degree _/9,_ of pulmonary extension when the Hering-Breuer reflexes set in; they also regulate the strength and rate of inspiration and aspiration. Z.I. Frankstein and Z.N. Sergeyeva appropriately pointed out that "the essential factor in the Hering-Breuer reflexes is that they are aimed at a prevention of the disruption of the gas composition of the blood" (1966:194). Carbonic acid plays a substantive role in providing the rhythmic nature of the respiratory center activity; in the hypocapnic state, intermittent impulsation in the fibers of the diaphragm nerve is changed to continuous pulsation. Priban (1962) holds that

arterial carbonic acid essentially affects the specific inhibiting neurons which, in turn, change the activity of the respiratory center. In fact, hypercapnia reduces the neuron sensitivity of the respiratory center (Gesell and Moyer, 1935). According to Barkroft's formulation, carbonic acid eliminates the inhibition, rather than actively stimulating the respiratory centers. Indeed, carbonic acid and comparable buffer solutions depress the impulsations when they act upon nerve fibers. When applied to the reticular formation of medulla oblongata, they cause breathing delay (Carpenter, 1963).

Banus et al., (1944) assumed the existence of two different systems in the respiratory center zone: one that reacts upon intracellular shifts of carbonic acid, the other zone reacting to reflex impulses received in the center. Under narcosis, the mechanism that is sensitive to carbonic acid is turned off, whereas the reflex mechanism continues to function.

Thus, it can be concluded that the respiratory centers have an immediate sensitivity to carbonic acid and to hydrogen ion concentration. The influence of these factors upon the operation of the center is of a complex nature and is predicated on the characteristic relationships between its functional elements. At the present time, it is still difficult to differentiate between these relationships and the functions of other chemosensitive structures of the brain which are mostly located in direct proximity to the respiratory center and were investigated only within recent years.

Specific Chemosensitive Brain Structures

The presence of chemosensitive zones in the brain was proven by observing the effects of lobelin and sodium cyanide upon respiration. The introduction of these preparations into the IVth cerebral ventricle produces a decrease of the respiration volume (Beckaert and Leusen, 1950), whereas a suboccipital injection produces the opposite effect (Winterstein and Wiemer, 1959). A perfusion of the IVth ventricle by veratridin = e also increases pulmonary ventilation (Loeschcke and Koepchen, 1958). /98

Numerous investigations appear to indicate the existence of specific zones in the brain that are sensitive to carbonic acid and to hyrogen ion concentration.

Based on their experiments, Euler and Soederberg (1952) concluded that the centrogenic effect of carbonic acid cannot be explained by a direct influence upon the neurons of the respiratory center, but rather by a stimulation of the true receptors, i.e., the first medullar neurons. The inspiration of a 10% CO_2 mixture activates the neurons of the retiform formation, even when afferent influences are absent (Bonvallet et al., 1956). Several investigators (Loeschcke and Koepchen, 1957; Loeschcke et al., 1958; Loeschcke, 1960; Mitchell et al., 1963; Loeschcke, 1965) demonstrated that the perfusion of the IVth ventrical of a cat's brain by solutions with a low pH or high P_{CO_2}, or the application of shields saturated by the same solutions to the ventricle's walls contributes to the animal's ventilation on account of the increased breathing volume. Apparently, the lateral surface of the medulla oblongata is the chemosensitive zone. Presumably, the chemoreceptors are located close to the soft meninx, or inside of it, and react to hydrogen ion concentration in the cerebrospinal fluid. Chemosensitive zones were also discovered in the diencephalon area (Masland and Yamamoto, 1962).

From these specific brain areas, the information is forwarded to the myelencephalic respiratory center proper (Comroe, 1967). We could assume that a certain concentration of hydrogen ions (as well as a certain concentration of carbonic acid), while stimulating the brain's chemoreceptors, eliminates the continuous stimulation of the inspiratory part of the respiratory center (Marshak, 1961). Moreover, in conjunction with a direct influence upon the center (as well as afferentation from arterial chemoreceptors), it also regulates the respiratory volume. Indeed, there exists a direct correlation between the ventilation, on one hand, and the C_H and P_{CO_2} of the cerebrospinal fluid, on the other hand (Michel and Kao, 1964). This relationship is particularly pronounced in non-narcotized animals (Pappenheimer et al., 1965).

Some authors (Heisey, et al., 1964) hold that about 40% of the ventilatory reaction to carbonic acid is produced by the increased hydrogen ion concentration of the cerebrospinal fluid, whereas 60% is produced by the effect of the same agents upon the peripheral chemoreceptors (carotid and aortic), and upon the respiratory center directly. Other investigators (Mitchell, 1966) suggest the opposite relationship. It must be kept in mind that during the inspiration of a hypercapnic mixture, the gain of P_{CO_2} in the liquor takes place considerably /99 later and slower than in blood (Bradley and Semple, 1962). A direct ion penetration from the cerebrospinal fluid to the first respiratory neurons of the reticular formation is also conceivable (Semple, 1965).

Some authors construe chemoreceptors of the ventro-lateral part of the medulla oblongata as only one of the central mechanisms responding to the variation of hydrogen ion concentration in the interior (Cozine and Ngai, 1967), or completely deny the rôle of liquor in the primary stimulation of the respiratory center under the influence of carbonic acid (Heymans et al., 1965). M.V. Sergiyevskiy also holds that the argument in favor of the "central" receptors is not convincing.

However, we feel that the existence of specific chemosensitive zones of the brain and their important role in hypercapnia reactions has been supported by sufficiently reliable experimentation.

Comparative Evaluation of Various Structures in the Perception of
Gas Composition

It follows from the preceding review that the existence of two principal groups of systems, sensitive to oxygen and carbonic acid pressure and participating in respiration control, has been established:

(1) arterial chemoreceptors of the aortal arch, particularly carotid sinuses;

(2) respiratory center chemoreceptors in conjunction with the specific chemosensitive structures of the brain.

The principal role of both receptor systems is to serve as an impulsation source, providing respiratory regulation in accordance with the metabolism requirements of the organism. This shows the importance of this "respiration analyzer" (Ayrapet'yants and Pogrebkova, 1963). Its sensor devices belong to interoceptors, and at the same time the afferent impulses from them are transfered to the actuating apparatus, which is closely connected to the ambient media and is part of the somatic system (Kocherga, 1965).

Apparently, the peripheral chemoreceptor mechanism is ancient, and is homologous to the "gas analyzer" of aquatic organisms. Actually, the branchial vessels in water-breathing vertebrates are the only elements that still maintain direct contact with the external media and are equipped with receptors that perceive the pressure of gases. With the transition of animals from water to land, these receptors became internal (arterial) and, naturally, acquired some new properties. It is difficult to agree that the high sensitivity of carotid /10C bodies in mammals, as compared with homologous formations of amphibia, contradicts the ancient origin of chemoreceptors of the carotid zone, as maintained by S.V. Anichkov and M.L. Belen'kiy (1962). It is that very origin of those formations that was newly confirmed by detailed comparative physiological studies (Ts.V. Serbenyuk, 1968). The significance of chemoreceptors in higher animals and in man is determined by the fact that they are at the "gate" of the arterial system. Similarly to baroreceptors, located in the same area, which provide a constant arterial pressure, the chemoreceptors maintain a constant gas composition of the arterial blood by way of reflex responses. The cruicial role of sinocarotid chemoreceptors in higher animals relates to the fact that the brain tissue requires a constant gas medium. At the same time, the immediate chemical sensitivity of the respiratory center was philogenetically developed on account of the increasing role of the central nervous system (CNS) (Chernigovskiy, 1947). The chemoreceptive apparatus, nonetheless, remains irreplaceable; e.g., under deep narcosis, when the chemical sensitivity of specific brain structures and of the respiratory center itself is depressed. Under such conditions, denervation of the carotid zones leads to breathing failure (Wett et al., 1934).

Being highly sensitive to threshold variations of the arterial pressure of oxygen, as well as to carbonic acid and hydrogen ion concentration, arterial chemoreceptors are the first elements to indicate these variations providing for an urgent adaptation of the breathing. Nonetheless, they rapidly adapt themselves to the effect of the irritant. The respiratory center and the receptor formations in the walls of the brain ventricles respond later, being a more stable regulatory mechanism (Winterstein, 1958; Okuneva, 1960). M.V. Sergiyevskiy (1961, 1963) holds that the cells of the cerebral cortex, along with carotid receptors, are also extremely sensitive to metabolism products, including carbonic acid. However, the immediate sensitivity of the respiratory center and of the reticular formation to carbonic acid is low, even though it is stable.

It was demonstrated above that respiration is controlled by a chemoreflexive as well as by a centrogenic mechanism, whereby the stimulation, caused by a relative oxygen "insufficiency" and the stimulation, caused by an "excess" of carbonic acid (even under normal rest conditions) do indeed coexist. The immediate sensitivity of the respiratory center to hydrogen ion concentration is higher than with chemoreceptors, and a denervation of the latter has little effect upon the hypercapnic reactions of the organism (Gemill and Reeves, 1933), especially when the inspired air is rich in carbon dioxide gas (Hesser, 1949). The oxygen insufficiency acts primarily through arterial chemoreceptors /101 (Cordier and Heymans, 1935; Wiemer et al., 1963; Comroe, 1967; and others).

The respiratory center of the medular reticular formation receives and integrates all stimuli that are forwarded from the receptor formations of various levels (Mitchell, 1966; Wiemer and Kiwull, 1966). Understandably, other parts of the brain also participate in this process, particularly the cerebral cortex (Sergiyevskiy, 1966, 1967). Temporary bonds are formed in the cerebral cortex; they provide for a rapid activation of adequate mechanisms of respiratory control which is explicitly manifested during muscular activity (Marshak, 1950, 1961). Cortex denervation reduces the sensitivity of regulatory mechanisms to carbonic acid, and disrupts the graduality of respiratory reactions under the influence of this agent (Ivanov and El'gort, 1966).

It should be generally kept in mind that the respiratory response to any given factor may be provided not by one mechanism, but by several interchange-able systems. For example, ventilation changes to air inspiration, containing 5-7% CO_2, in anaesthesized rats disappear only with short-range denervation of carotid glomera (area postrema) in the region of thalamus anteriori corpora quadrigmina, or of pons varolii anteriori and the mastoid bodies. In fact, the retention of at least one of these formations makes the respiratory response possible in its entirety (Masland and Yamamoto, 1962).

In spite of the extreme complexity of the mechanisms that participate in reactions to such factors, as hypoxia and hypercapnia, the activity of this "optimizing" system (Priban and Finchham, 1965) is regular to the extent that it is possible to accurately predict shifts in the respiratory functions under certain influences, including the formulation of appropriate models (Grodins, 1964; Yamamoto and Raub, 1967). All ventilatory stimuli that participate in the regulation can be interpreted as elements of a closed circuit, converging upon a certain common field in the CNS (central nervous system), where they are transformed into an output signal. The CNS is based on feedback to the re-ceptor devices, and hence is extremely sensitive (Tenney, 1963).

It has been pointed out before that there exists a positive interaction between the different stimuli, i.e. oxygen deficiency, carbonic acid excess, and hydrogen ion concentration; it appears that these stimuli amplify their respective influences upon respiration. As a result, the ventilatory response under certain combinations of hypoxia and hypercapnia is greater than the arith-metical sum of the effects of each of these factors, acting separately (Nielsen and Smith, 1951; Loeschcke et al., 1963; Cunningham et al., 1964; Honda et al., 1965; Malmejac et al., 1966). Accordingly, under hyperoxia, the respira-tory reactions to carbonic acid are attenuated (Loeschcke and Gertz, 1968; Lam- /102 bertsen et. al., 1963; Downes and Lambertsen, 1966).

The interaction between hypoxic and hypercapnic stimuli is elucidated by different schools of thought. Some investigators demonstrated the disappearance of this interaction in animals after denervation of the carotid receptors

(Malmejac et al., 1966). Other authors hold that reciprocal amplification of the hypoxic and of the hypercapnic stimuli is essentially of a central origin (Wiemer and Kiwull, 1966), or else it requires a "state of central stimulation" which takes place specifically during muscular activity (Tenney and Brooks, 1966).

Incidentally, hypoxic-hypercapnic interaction is directly related to respiratory control during muscular work. Muscular activity is associated with a strong increase of oxygen consumption and a rising level of carbonic acid and of other acid products in the blood. Such a combination is the most adequate factor for respiratory stimulation; this explains the phenomenon of the strongly pronounced ventilatory reaction to hypoxia in conjunction with hypercapnia. A detailed analysis of this complex and important problem lies beyond the framework of this study, because here we are dealing with reaction to shifts in the internal medium. However, it should be pointed out that it is during muscular activity that apparently the most complete interaction between peripheral and central devices, perceiving chemical shifts in the organism, takes place. The ventilation is brought into an exact balance with the shifts of the gas composition of mixed venous blood (Yamamoto and Edwards, 1960; Riley et al., 1963; Hashisuka, 1965), i.e., the level of oxygenation-reduced process in the organism. This explains the aforenamed numerous attempts to prove the existence of "mixed venous" chemoreceptors. Respiratory control during muscular activity is so perfect that (provided that the load is not excessive), the alveolar P_{O_2} as well as oxygenation and blood P_{O_2} are almost unchanged, as compared to a state of rest (Konradi et al., 1934; Voytkevich, 1955; Hesser and Mattel, 1963; et al).

It appears to us that above all the chemical shifts in the internal medium that occur during muscular activity are adequate stimulation of the chemoreceptive devices that participate in breathing control. Indeed, if venous blood is directly enriched by carbonic acid, the ventilatory reaction turns out to be the same as with corresponding hypercapnia, caused by inspiration of a mixture containing a large amount of carbon dioxide (Lamb, 1966, 1967). Thus we have complete compensation for the gas regime during moderate muscular

activity, as compared to incomplete compensation during inspiration of changed gas mixtures (Dornhorst, 1963).

Indeed, the function of all receptor mechanisms, that respond to the pressure of the respiratory mixture in land vertebrates, consists in the perception of those shifts in the chemism of the interior medium which take place during work and other metabolic changes. For practical purposes, the organism is not exposed to significant variations of the gas composition of the external media. Using modified respiratory media, we act only upon individual links of the "optimization system". And this system, in turn, is designed to eliminate only the endogenic shifts in gas composition of the internal medium. Thus, when mixtures with carbon dioxide are inspired, the signalization from chemosensitive devices (carotid and "brain" chemoreceptors, cells of the respiratory center proper) is convereted into an "output signal" which causes an increase in ventialtion that is sufficient to wash out the excess carbonic acid with ordinary air. However, since the expired mixture is enriched by carbon dioxide, only a "compromise" reduction of hypercapnia is attained (i.e., provided that the mixture's P_{CO_2} is less than the alveolar), and alveolar P_{CO_2} is maintained on a more or less elevated level (Tenney, 1963).

It follows that in view of the physiological properties of chemosensitive devices, a compensation of the shifts caused by oxygen insufficiency or excess carbon dioxide in the respiratory medium (especially if these factors are acting separately), strictly speaking, cannot be complete. Using such gas mixtures, we are only partially modelling the reactions by means of which the organism maintains a constant internal gas medium. However, the specific purpose of the "gas analyzer" of higher animals is the perception of the shifts of chemism in the internal media which, in view of the varying intensity of the metabolic processes, require an appropriate restructuring of breathing.

ON THE AFFERENT LINK IN THE GAS PREFERENCE RESPONSE

It was demonstrated that not all reactions (e.g., hyperventilation, etc.) to a changed respiratory media are accompanied by general behavioral responses

in animals, or by a differentiating response in man. Gas preference is manifested only when the gas regimen of the organism is noticeably disrupted; this manifestation, obviously, is caused by some stimuli from the internal medium. The question hence arises: which perception devices emit these stimuli?

From the preceding discussion it should be apparent that the appropriate impulses could not originate in the upper respiratory tract or from the lungs. The following characteristic features of gas preference also support this contention: /104

(1) A rather long latent period of the response of choice and differentiation of the mixtures, measured in minutes (and not in seconds, as for olfactory reactions);

(2) Absence of direct feedback between gas preference in man and the composition of respiratory media selected by man, as demonstrated in experiments with a fixed breathing regime.

These experiments demonstrated that man's ability to differentiate between gas compositions is related to stimulations from the vascular bed or tissues, rather than from the respiratory passages.

Role of Sinocarotid Chemoreceptors

Inasmuch as the role of sinocarotid chemoreceptors (essentially glomera of the carotid sinus) is generally recognized in almost all reactions, involving a changed gas medium, we attempted to estimate their role in gas preference responses. To this end, we performed experiments involving the denervation of sinocarotid arteris of white rats.

The bifurcation of one of the carotid arteris was exposed in the animals under nembutal. To prevent unfavorable reflex reactions during tissue surgery, the area was infiltrated with a 0.5% novocaine solution. The adeventitia

of the carotid sinus was thoroughly treated with phenol (10%). The same was performed on the other carotid. The prophylaxis for pneumonia, which is a frequent occurrence with this type of surgery, was done by repeated intramuscular penicilline injections. After three to five days, the animal was fit for conventional experimentation.

The rats that were used as control animals for the "denervated" rats, were subjected to the same operation, with the exception of artery treatment by phenol.

Figures 31 and 32 indicate that a denervation of the sinocarotid zone produced a considerable effect upon the *hypoxy gas preference in rats.*

The denervated animals did not react to weak hypoxy (14% O_2 in nitrogen) whereas in the control animals there was a tendency (however weakly pronounced) to a negative choice reaction. The control animals reacted in a clearly negative manner to a medium containing 10.5% O_2, whereas rats exposed to sinocarotid denervation reacted much less; in fact, their reaction did not even reach a statistically appreciable level. A strictly hypoxial mixture (7% O_2 in nitrogen) was avoided by both groups of rats almost equally.

It follows that chemoreceptors of carotid sinuses play a considerable role in gas preference reactions in rats, as compared to moderately hypoxic mixtures. An almost entirely negative reaction to oxygen deprivation is retained after these receptors are eliminated. This appears to indicate that the upper /105 segments of the CNS receive signalization on the hypoxic state of the organism not just from the receptors of carotid glomera, but also from some other reflexogenic zones. At extreme stages of oxygen starvation, the latter can also completely substitute for the chemoreceptor function of carotid arteries.

Rats, subjected to sinocarotid denervation, barely reacted to moderate admixtures (5%) of carbon dioxide; the control animals began to display a negative reaction. A pronounced hypercapnic medium (CO_2 9%) produced a negative reaction in the denervated animals as well; however, this reaction was weaker
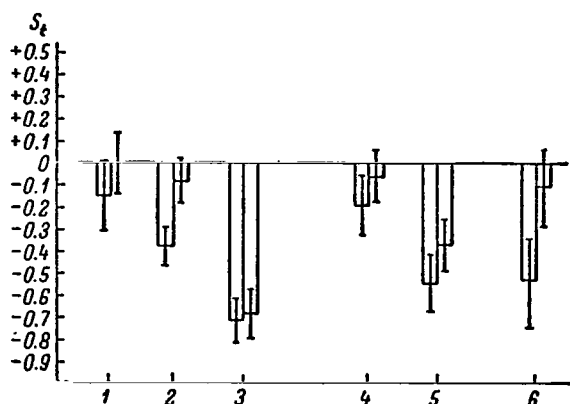
Figure 31. The effects of the sino-carotid denervation upon the gas preference of rats. The data are averaged from 20 animals. Each pair of columns represents: the left column - control-operated animals. The right column - animals that survived carotid sinus denervation. Vertical column - selection index of the different zone $S_{(t)}$; Horizontal column - gas composition in the different zones: 1 - 14% O_2; 2 - 10.5% O_2; 3 - 7% O_2; 4 - 5% CO_2; 5 - 9% CO_2; 6 - 10% O_2 + + 3% CO_2.

than in the control animals.

Thus, carotid sinus receptors also participate in the behavioral reactions to hypercapnic atmosphere. As expected, in the absence of these receptors, the reaction to carbon dioxide does not disappear entirely. We know now that chemosensitive areas of the brain also serve as a source of hypercapnic signalization.

When the same mixture (9% CO_2) was administered with a hypoxia background (11.5% O_2), then the negative reaction of rats with eliminated sinocarotid receptors was reduced even more. Possibly, the depressing action of oxygen /106 starvation upon the nerve centers is more pronounced in the presence of impulsation from the peripheral nerve centers. After sinocarotid denervation the animals stopped avoiding a combined hypoxic-hypercapnic medium (10% O_2 + + 3% CO_2); this proves the participation of the chemoreceptors of the arterial bed in the mechanism of positive interaction of the hypoxic and hypercapnic stimuli.

These data support the fact that the chemoreceptors of the sinocarotid zone are one of the receptor elements of the gas preference reaction chain. It is of interest, as pointed out by V.G. Kassil', A.M. Ugolev, and V.N. Chernigovskiy (1964), that the carotid glomera play an important role in the behavioral reactions of selecting preferred food products by the organism.

It follows that these chemorectpor zones participate in the chemism regulation of the internal medium in the broadest sense. Indeed, S.V. Anichkov and

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Figure 32. A kymogram of the movements of a rat in a hypoxia gradient (10 to 21% O_2) after sinocarotid denervation. There is no notable avoidance of the hypoxic zone (compare with Figure 6; notations are the same).

M.L. Belen'kiy (1962) demonstrated conclusively that reflexes, stemming from carotid glomera, affect not just the respiration, but also a number of conjugated functions such as hydrocarbon metabolism and, in the final analysis, are directed toward maintaining the energy resources of the organism.

So far, it is not yet entirely clear as to what other perceiving devices participate in gas preference reactions. While the receptors of brain ventricles are also sensitive to carbonic acid, when it comes to hypoxia reations, we can only estimate them in terms of the chemoreceptors of the arch of the aorta. The latter, as generally believed (Chalmers, et al., 1967; and others) play a considerably lesser role than carotid receptors. However, this has been established on laboratory animals — dogs, cats, and rabbits, which are the conventional objects for sinocarotid denervation. The problem of the possible role of aortal receptors in the respiratory regulation of rats has not been touched upon in the literature that is available to us. It is conceivable that animals react not just upon peripheral chemoreflex afferentation, but /107 also on some shifts of a secondary nature (circulatory and metabolic) which occur as a result of oxygen starvation in various systems of the organism, including the brain (Sanotskaya, 1962; Cohen, et al., 1967).

The differentiation of respiratory mixtures by man is even more complex.

It was pointed out by A.B. Gandel'sman and his staff (Gandel'sman, 1965; Gandel'sman, et al., 1966) that man can estimate his hypoxic state in exact accordance with the actual blood oxygenation decrease, i.e., apparently based upon some adequate introceptive signalization.

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Gutz, et al., (1966), recently undertook a detailed investigation of the role of arterial chemoreceptors in the respiratory response of man. To block the sinocarotid and aortic chemoreceptors, they introduced lignocain into the subject's cranium base, in the area of the IXth and X^{th} nerve trunks. After a control period (air respiration), the subjects were unnoticeably switched to respiration of a hypoxic mixture (8% O_2 in nitrogen). It was found that blocking substantially reduced the ventilatory response. However, during breathing the mixture, in the subject's own words, he experienced "the usual pleasant sensation of hypoxia".

In another experiment, the same subject, upon identical blocking of the arterial chemoreceptors, was given a mixture containing 3% CO_2 in oxygen. The experiment was performed under conditions of countercurrent breathing with a gradual increase of carbon dioxide concentration in the respiratory medium. The ventilatory response in this instance also went down substantially, as compared with the control experiment (prior to the blocking). Denervation of the sinocarotid and aortic receptors apparently also affected the sensations during hypercapnia: there was no desire to "expand the chest", and the subject could continue to breathe the carbon dioxide mixture for a considerably longer time that in the control experiment. The authors correctly explain that by the blocking of the afferent fibers of the pulmonary branches of n. vagus, which participate in the Hering-Breuer reflex, rather than by chemoreceptor denervation.

A flaw in both of the described experiments is that each one is a singular experiment. Moreover, they were performed on a subject who was apparently fully aware of the investigation in progress. Unfortunately, we were unable to find references to similar studies in the literature.

The current state of the art leads us to surmise that the receptor link in gas preference reactions in man includes, in addition to arterial chemoreceptors, some other receptor devices. As in animal reactions, once could conceivably /108 assume the chemosensitivity of certain areas of the brain, as well as the reception of secondary hypoxic and hypercapnic shifts in tissues primarily in the CNS itself.

Common Mechanisms of Differentiating Respiratory Media.
Gas Preference and Dyspnoea

It appears to us that mechanisms of gas preference cannot be simply treated as the results of impulsation from a certain reflexogenic zone. Apparently it is not just the sensory formations, described in this review, which serve as the receptor link in compensatory reactions of the respiratory and of related systems that participate in this process.

One characteristic of the reactions of differentiation and selection of gas media is in the long latent period, measurable in terms of minutes. These reactions set in only after the beginning of compensatory reactions which become evidenced after only a few seconds. Gas preference thus emerges as a result of an integrating function of the CNS.

Apparently the phenomena develop in the following order. The inspired mixture with changed composition changes the pressure of the gases in the alveolar air and subsequently in the blood. These changes are perceived by arterial chemoreceptors and by chemosensitive areas of the brain, including the cells of the respiratory center. This, in turn, activates a number of adaptive mechanisms of respiration, blood circulation, and other functions. If in this manner a more or less complete compensation of the gas regimen shift in the internal media is attained, then the stimulation level from the aforementioned receptive zones does not increase, or else it even decreases. In this instance, there are no other general behavioral reactions of the organism to the given media. Specifically, man does not differentiate it from normal air. In the same instance, when the adaptive reactions are obviously insufficient, and the blood and tissues retain considerably changes of the gas regimen, the amplified impulsation from appropriate receptor devices grows. The response becomes amplified by the afferentation, caused by the development of secondary metabolic shifts in the organism: change of the pH of body fluids, accummulation of insufficiently oxygenized products, etc. Such an unusual afferent signalization, combined with a changed working regimen of the respiratory muscles and other systems, is the initial stimulus for a negative reaction to the inspired gas mixture.

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Apparently a negative reaction to the gas media can also take place in instances when the compensation is satisfactory, but is attained as a result of excessive stress of the adaptive mechanisms, specifically by a drastic increase of the energy consumption for respiratory work.

Here we should particularly consider man's formulation of sensations when breathing mixtures that are being rejected by the body. Regardless of the nature of the mixture (hypoxic, hypercapnic) the test subjects most frequently state, "It's difficut to breathe", "Not enough air", etc. But those are the complaints of dyspnoea patients! It would appear to us that dyspnoea symptoms coincide with the negative gas preference reactions not only in this, apparently totally external symptom, but also in their very substance.

As is known, dyspnoea complaints occur not just in a certain pathology of respiration, blood circulation, metabolism or CNS functions; they are also registered by healthy individuals exposed to heavy muscular loads, or upon climbing to high altitudes. The pathogenesis of dyspnoea is by far not always clear.

There is even no clear and precise formulation of the concept of dyspnoea. M.V. Chernorutskiy (1954) and G.F. Lange (1958) distinguished between subjective dyspnoea (sensation of insufficiency of breathing and hard panting) and objective dyspnoea (acceleration of breathing and a change in its nature). Some authors (Garbinski, 1967; and others) still maintain the same differentiation. Attempts were made to define dyspnoea as a unique phenomenon, manifested both subjectively and objectively (Myasnikov, 1952; Tushinskiy, et al., 1960). A.G. Dembo (1966) pointed out that dyspnoea is "hyperpnea or inadequate hyperventilation".

However, we must keep in mind that dyspnoea is not always accompanied by hyperpnea. On the other hand, it is incorrect to refer to all hyperventilations as dyspnoea. It is also very difficult to decide on the adequacy of ventilation under changed conditions of gas exchange. There appears to be no clean-cut connection between dyspnoea and the gas composition of the blood. Generally, the dyspnoea phenomenon does not coincide with the concept of a respiratory

insufficiency as a discrepancy between the respiratory function of the organism and the gas exchange requirements in the broad sense of this definition (Dembo, 1957, 1966; Doroshchuk, 1965; Arakcheev, 1967).

For this reason, it appears to us that the viewpoint of those clinicists who relate dyspnoea specifically with the "subjective" aspects of breathing impairment, i.e., with the respective complaints of the patient, is more justified. In this sense, dyspnoea is a manifestation of the recognition of ventilation difficulties (Comroe, et al., 1956).

What are the difficulties involved? Some investigators hold that the source of unpleasant sensations during dyspnoea is in the accummulation of metabolism products in respiratory muscles under stress (Garbinski, 1967). According to N.S. Magazinnik (1962), dyspnoea patients have a considerably higher /11 energy consumption for pulmonary ventilation (see Chapter III regarding the precise perception of increased resistance to breathing in man). The author relates dyspnoea with increased respiratory work, yet he found no distinct relationship between them. As we pointed out, there is no distinct relationship between dyspnoea symptoms and variations of the blood's gas compositions, either.

Apparently, in some instances, the discrepancy between respiration and the conditions of gas exchange, as well as overstress of the adaptive mechanisms, are reflected in the higher sectors of the CNS which integrate the signalization from proprioceptors of the respiratory muscles, the chemoreceptors of vessels and tissues, etc. That is when conscious negative reaction to these conditions is expressed in the form of complaints of impairment of breathing, lack of air, etc. I.M. Sechenov (1866) classified such uncertain feelings (on the order of hunger or overfilling of the stomach) in the category of self-conscious phenomena which allow man to respond to impairments of his body functions.

Gas preference reactions belong in the same category of phenomena. In terms of mechanism, negative gas preference reactions and dyspnoea apparently conicide. We saw that negative reactions in man to different gas mixtures as well as dyspnoea symptoms may occur with normal VRM (in experiments with a

fixed respiratory regimen), and conversely, may be absent in hyperventilation. It should be specified that dyspnoea is a negative reaction to non-compensated or difficultly-compensated disturbances of the gas regimen of the organism, caused by *internal* reasons (e.g., an obstructive pulmonary affliction or excessive muscular activity). A negative gas preference reaction is related to similar disturbances, caused by *changed respiratory media.* Incidentally, dyspnoea complaints in mountains should be considered as a negative gas preference to reduced partial oxygen pressure in the atmosphere. On the other hand, normal air, as we saw, can also cause typical dyspnoea complaints if a completely healthy subject is exposed to an alien respiratory regimen.

Taken in this frame of reference, studies of gas preference can contribute to the understanding of the mecahnism of respiratory impairments, both under physiological and pathological conditions.

Chapter VI

FACTORS DETERMINING THE DIFFERENTIATION AND THE CHOICE OF THE

RESPIRATORY MEDIUM BY THE ORGANISM

Gas preference manifestations, similarly to other complex behavioral re-
actions, are determined by many internal and external factors. Here, we will
only consider some of the most important of these factors.

DEVELOPMENT AND TRAINING OF GAS PREFERENCE REACTIONS

The primary question, both of theoretical and practical interest, is —
are gas preference reactions congenital, or are they formed as a result of re-
peated exposures to an unusual respiratory environment? The possibility of
training or influencing these reactions is closely related to this problem.

Since higher animals under normal conditions do not encounter substantial
deviations of the respiratory environment from normal, it could be assumed that
gas preference of Earth vertebrates is not congenital.

Indeed, observing the active selection of preferred gas mixtures by
animal and man, it becomes apparent that the choice is formed by repeated
sampling of the offered mixtures. An animal, placed into a gas gradient
chamber, usually makes several runs from one end of the chamber to the other
until it selects the preferred zone. Man, in most instances, is switched dur-
ing the selection from one mixture to another.

Apparently, temporary bonds are formed during this sampling between the introceptive signals, considered in the preceding chapter, and the external stimuli. The differentiation reaction of gas mixtures is formed on the basis of these bonds. If such were the case, repeated exposures to the same mixtures would have to improve the differentiation ability of the organism, or in other words, strengthen the gas preference.

Dynamics of the Development and Reversal of Hypoxic and Hypercapnic Gas Preference in Animals

To verify this assumption, experiments were performed on white mice, involving repeated exposures to hypoxic gradients (Breslav, 1965c).

The animals were exposed at constant gradient for 30 minutes daily over a five-day period in a gas gradient chamber. Thereupon the gradient was reversed, i.e., a hypoxic media was formed at the air end of the chamber, whereas the formerly hypoxic zone became undifferentiated. An additional three to five exposures were performed under these conditions, until the formerly observed reaction was restored. For an adequate evaluation of the gas preference, the selection time, i.e., the time between the beginning of the exposure and the moment of selection of the preferred environment by the animal, in addition to the differentiated mixture index (S_t), was also taken into account. In order to evaluate the effects of the respiratory experiments upon the general condition of the animals, they were weighed daily (in this manner young mice make it possible to register eventual impairments of their growth).

Several series of experiments were performed in the gas gradient device, using different gradients. We will analyze the three most typical experimental variants: a modified, strong, and a very drastic oxygen reduction in the differential zone. Ten mice were used in each variant.

A moderately hypoxic environment (12.5% O_2) caused a statistically significant preference of the indifferentiated zone of the chamber by the animals (see Figure 33). The negative choice index for the hypoxia zone was lower during

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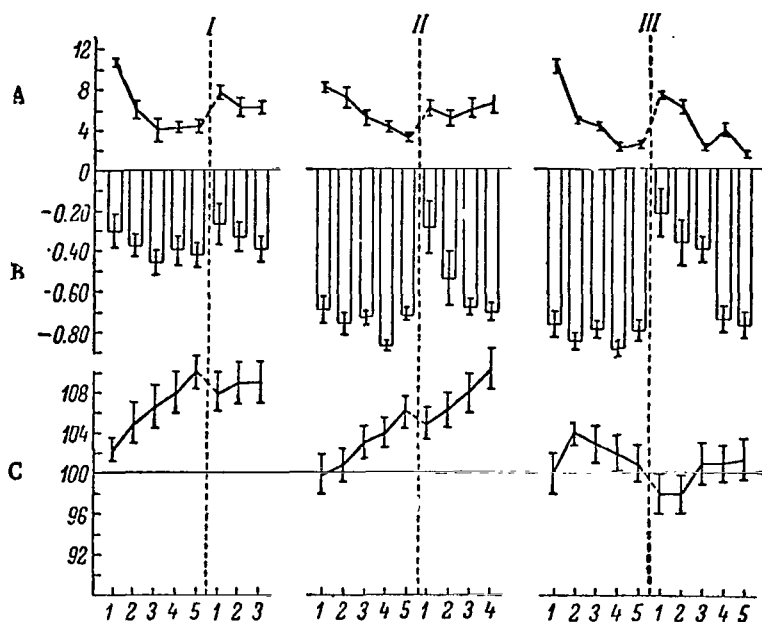
Figure 33. Dynamics of hypoxic gas preference in mice during repeated exposures to the following oxygen content in the differentiated zone: (I) - 12.5%; (II) - 7.5%; (III) - 2%. The data are averaged for each group of 10 animals. A - time of choosing the preferred zone, in minutes; B - selection index of the differentiated zone (S_t); C - body weight on the following day after the exposure, in % of the weight on the initial day. The horizontal lines show the numbers of exposures; the dashed vertical lines show the ordered reversal change of the gradient in the device.

the first exposure, and higher during subsequent exposures. At the same time, the mice began to avoid the hypoxic end of the chamber sooner starting with the second exposure. Judging from the gain in weight, the condition of the animals during the experiments remained normal. A reversal of the gradient direction of the device reduced the preference of the undifferentiated zone, extended somewhat the time of choice, and produced a slight decrease of the body weight. During the third exposure, these shifts were almost smoothed out.

Unquestionably, this adequate avoidance reaction of the hypoxic zone in mice is a conditional reflex type reaction. This is supported primarily by the

fact that this reaction is not manifested immediately,but involves a certain period of choice, amounting to 8 to 11 minutes, during the initial exposures. During such time, the mouse was able to run into the hypoxic zone 10 to 12 times and to be exposed to oxygen starvation to a certain extent. Even though the effect in each instance was measurable in terms of seconds, one must consider the insignificant oxygen reserve in the body of such a small animal, taking into account the relatively high level of its gas metabolism. In addition, a short-range variation of the composition of the inspired air acts even stonger than a long-range variation (Hornbein et al., 1961). After numerous runs between the hypoxic and the air ends of the chamber, the animal developed an avoidance of the hypoxic zone. Subsequently, the reaction was enforced and accelerated, representing to a certain extent a reflex to a location. When the gradient was reversed, the animal developed a new reaction with much more difficulty than the initial reaction. The modified conditions were now in conflict with spatial relationships, that were already formed. This reversal is not on easy process for the animals, and this is probably best evidenced in the temporary impairment of the weight gain.

Thus, mice develop a negative reaction to a moderate reduction of the oxygen content in a differentiated environment (known as compensated hypoxia); this negative reaction can be reversed relatively fast.   /114

Exposure in a gas gradient chamber,where the oxygen content in the hypoxic zone was reduced to 7.5%, was accompanied by a considerably stronger reaction. By and large, the dynamics of consecutive exposures and of gradient reversal did not substantially differ from the one described above. Notably, the restoration of choice after the reversal took slightly longer; the longer selection time was retained until the fourth exposure.

When oxygen concentration was drastically reduced (up to 2%), the choice index at the hypoxia end of the gas gradient device varied at about -0.9, whereas the selection time during five exposures was reduced from 10.2 to 2.0 - 2.4 minutes. Beginning with the second or third day of the experiments, the gain of body weight was replaced by a tendency to some loss of weight. A

reversal of the gradient direction caused a considerable decrease of the animals' reaction to the hypoxic media, and also resulted in a loss of weight. These indexes began to approached the initial figure only starting with the fifth exposure.

Thus, with a more pronounced decrease of the oxygen concentration in the differentiated environment that caused non-compensated hypoxia, the animals' reaction is not only more pronounced, but it is also formed quicker. At the same time, its reversal, when the gradient direction is reversed, is more difficult. Apparently, the reflex to location that is formed here is more stable. Moreover, the inhibiting effect of oxygen starvation may affect the unconditional reflexes, including chemoreceptive reflexes (Pozdnyakova, 1963), as well as the conditional reflexes (Zvorykin, 1953; Bullard and Snyder, 1961; Doronin, 1963). This influence may have inhibited the reversal of the reaction to changed conditions.

It appears to us that the impairment of the normal functioning of nerve centers accounts for instances of the atypical paradoxic reaction, observed in 10 to 15% of the experimental animals (Table 2). Thus, one animal (Mouse No. 802) during the first exposure preferred the hypoxia zone, rather than the air zone. The experiment was interrupted when the animal had a convulsive seizure during one of its runs to the hypoxia end (2% O_2). During subsequent exposures, the mouse quickly chose the undifferentiated area of the gas gradient device, where it stayed almost for the entire duration of the experiment; this was accompanied by a progressive loss of weight. When the direction of the gradient was reversed, the mouse stayed mostly near the hypoxia zone during the first two exposures, and displayed a weak preference for the air zone only during the third exposure. The loss of body weight progressed strongly; the animal died displaying typical symptoms of general exhaustion. Another animal (Mouse No. 806) also preferred the hypoxia zone during the first exposure; this animal also went into convulsions. When the gradient during the first and /116 third exposures was reversed, the mouse again chose the hypoxia zone. A weak preference to air environment was apparent only during the fourth and fifth exposures. A reversal caused a considerable reduction of body weight which slowed down only at the end of the experiment series.

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TABLE 2 ATYPICAL REACTIONS OF MICE TO A STRONG HYPOXIC ENVIRONMENT (2% O_2)

Index	Exposure at initial gradient					Exposure after reversal of gradient direction				
	1st	2nd	3rd	4th	5th	1st	2nd	3rd	4th	5th
Animal No. 802										
Choice (in minutes)	—	5	4	1	1	2	4	1	—	—
Choice index of the differentiated zone (S_t)	—*	—0.90	—0.96	—0.96	—1.00	+0.33	+0.33	—0.10	—	—
Body weight the day following the exposure (in % of the initial exposure day)	102.1	104.1	100.9	98.4	98.4	88.0	77.5	—**	—	—
Animal No. 806										
Choice (in minutes)	—	—	6	—	—	1	1	1	2	1
Choice index of the differentiated zone (S_t)	—*	—*	—0.86	—*	—0.33	—*	0	+0.30	—0.12	—0.20
Body weight the day following the exposure (in % of the initial exposure day)	102.8	107.0	105.4	105.0	100.7	96.9	94.6	87.2	82.2	81.4

* Animal remains in the hypoxic zone, convulsions set in and, as a consequence, the exposure is interrupted;

** Animal perished a few hours after the exposure.
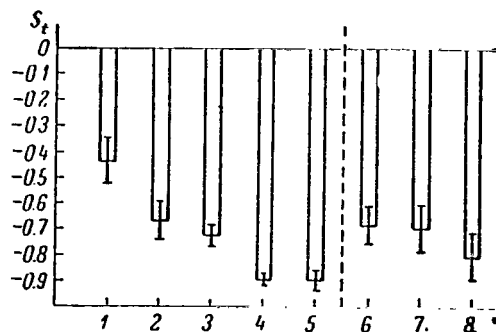
Figure 34. The dynamics of hypercapnic gas preference in rats with repeated exposures with 12% carbon dioxide in the differentiated zone. Data averaged for 10 animals.
Columns: choice index of the differentiated zone, (S_t);
Horizontals: numbers of exposures; Dashed line: reversal of gradient direction in the device.

One could assume that some individuals developed a peculiar neurosis in such instances, in view of difficulty of developing an adequate reaction to a strongly hypoxic environment. This neurosis became extremely acute as a result of the "collision" caused by the reversal of the gradient direction; this was accompanied by a drastic impairment of the trophical system and even by the death of one of the animals.

These findings support the assumption regarding the participation of the conditioned reflex mechanism in the formation of hypoxic gas preference. It agrees with known facts in the development of conditioned respiratory and other reflexes in animals under the influence of undifferentiated stimuli in conjunction with hypoxia (Arkhangel'skaya and Segal', 1954; Madarsz et al., 1965; et al.)

Similar regularities were discovered with respect to reactions to hypercapnic mixtures. As demonstrated in Figure 34, the negative reaction of white mice to an environment containing 12% CO_2 becomes stronger. Gradient reversal temporily reduced this reaction to a small extent.

Thus, temporary bonds are established during the formation of behavioral /117 reactions tc excess carbon dioxide in the environment. This again is in agreement with the data available on the possibility of developing conditional respiratory reflexes, based on hypercapnia (unconditioned stimulus), in conjunction with any exteroceptive signals, including the mechanics and environment of the experiment (Krasnov, 1953; Pogrebkova, 1958; Golodov, 1959; Ivanov and El'gort, 1966).

Figure 35. Dynamics of hyper-
capnic gas preference in man
with repeated exposures to a
mixture containing 2% CO_2.
Data obtained from 6 subjects.
A - selection index of the
differentiated mixture (S_t);
B - ratio (in %) of subjects
who identified the differen-
tiated and undifferentiated (air)
mixtures correctly (1), in-
correctly (3), and those who
did not differentiate between
the mixtures (2). Horizontal
line - number of exposures;
vertical dashed line -
beginning of information from
the test subjects regarding
the correctness of their
identification of the mixtures.

On the Possibility of Training Man to
Differentiate Breathing Mixtures

The discovered tendency of gas preference
reactions in animals to strengthening and con-
solidation, when the organism is repeatedly
exposed to a hypoxic or hypercapnic environ-
ment, indicates that it is theoretically pos-
sible to train for a differentiation of breath-
ing mixtures.

An example are the two following consecu-
tive experiments with recurrent breathing in
a closed system, i.e., under conditions of
gradually increasing hypoxia. The experiments
were conducted using the same method as des-
cribed in Chapter II.

During the first experiment, most of the
subjects not only did not have any sensations
related to oxygen insufficiency during re-
current breathing, but were even unable to
switch themselves to atmospheric air up to
the moment of loss of consciousness. In the   /119
second experiment, all subjects were able to
identify the sensation of oncoming hypoxia;
and most of the subjects, at the end of the
experiment, actively switched to air, being
aware of their inability to further breathe
the hypoxic mixture.

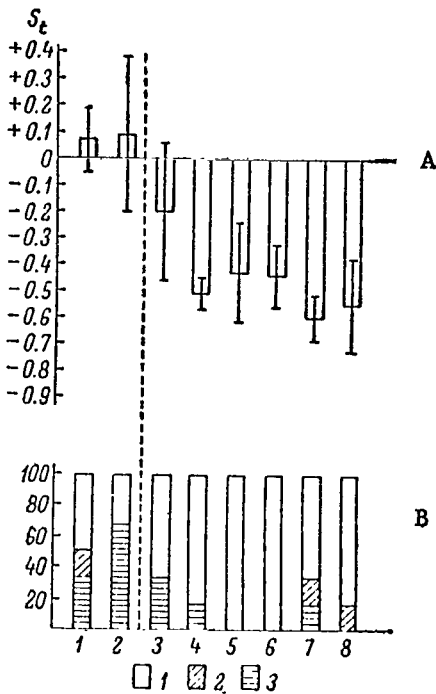Notably, A.B. Gandel'sman (1965) pointed out that man indeed has the
ability to estimate the degree of hypoxemia at any given moment by means of
repeated exercise. "The physiological nature of the phenomenon of improving

the accuracy of introceptive analysis appears to be predicated on a complex perception of the time dynamics by the subject, remembering the perceptions during the direct stimulation of the tissues (specifically the nerve centers), and remembering during the chemoreceptor stimulation of vascular and reflexogenic zones" (Gandel'sman and Verkhalo, 1966:201).

With a repeated encounter of hypoxic mixtures, the preference becomes more pronounced. Thus, in one of the groups, consisting of 12 subjects, who were not yet exposed to hypoxia mixtures, only 9 subjects showed a negative reaction to a mixture containing 9% O_2. In another similar group, which was exposed to various hypoxic environments, the same mixture caused a negative reaction in all 12 test subjects.

To establish the possibility of training man's capabilities to differentiate the admixture of carbon dioxide in the respiratory environment, we exposed a group of six men on several occasions to the same pair of gas mixtures: an undifferentiated one (air), and a differentiated one, which contained up to 2% CO_2 with a normal oxygen content. After five minutes of such exposures, this CO_2 concentration, as demonstrated in Chapter II, becomes a sub-threshold concentration with respect to man's gas preference.

Indeed, during the first exposure, only half of the test subjects displayed a negative reaction to this mixture; during the second exposure, the number of subjects with a negative reaction was even lower (Figure 35). In future tests, the following problem was posed before the subjects: learn to distinguish between a differentiated mixture, and an undifferentiated mixture. At the end of each test, each subject was informed whether or not he correctly determined which of the buttons of the control panel turned on the hypercapnic mixture, and which of the buttons turned on the air (the connections between the buttons and the mixtures were varied at random). As indicated on Figure 35, starting with the second or third experiment, this information led most of the subjects to a correct differentiation of the mixtures. /120

Naturally, some of the test subjects erred not only in that they wrongly identified the offered mixtures, by also displayed a perverted respiratory reaction. Thus one of the test subjects (female) had a completely normal and moderate reaction during the first experiment to a 2% content of CO_2, whereas during the fourth experiment she judged air to be a differentiated mixture, while she was obviously avoiding air during this experimentation. At the same time, the breathing of air caused a pronounced hyperventilation, whereas the inspiration of a hypercapnic mixture produced hypoventilation. Thereby, the respiratory changes during the switchings took place instantaneously, when the mixture composition could not have affected the respiratory mechanism (Figure 36). Obviously, we are dealing here with a suggested respiratory response. Being familiar with the physiology of respiration, this particular subject (as opposed to others), following her personal verbal estimate of the mixtures — in this instance an incorrect one — involuntarily simulated (in an exaggerated fashion) the ventilatory response to a mixture that appeared to her to be a differentiated one. Incidentally, V.I. Voytkevich (1952) noted adequate respiratory response to a verbal signal on the forthcoming application of a hypoxic mixture (command: "Poor mixture coming up!") in her test subjects.

In Chapter IV, we emphasized the role of a verbal self-report on the mechanism of man's gas preference reactions. The aforenamed facts indicate that verbal signalization has a decisive influence also in the training of man's capability for the differentiation of respiratory mixtures.

INDIVIDUAL AND AGE CHARACTERISTICS

Individual Variability of Gas Preference

In both animals and man, gas preference responses seem to be subject to considerable individual differences.

Among mice and rats we have found individuals which do not even react to severe changes in the gas composition in the differentiated end of the gas gradient instrument. As has already been said, such animals quite often died

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A

$21\% O_2$ in N_2 $2\% CO_2$ in air $21\% O_2$ in N_2 $2\% CO_2$ in air $21\% O_2$ in N_2

6.4 5.0 4.4   4.4 4.6 4.4 5.4 5.0 6.2 7.0   5.4 3.4 4.0 6.0   8.2 7.5 5.3   4.8 3.0 3.6 4.2 5.4 3.2

B

$21\% O_2$ in N_2 $2\% CO_2$ in air $21\% O_2$ in N_2 $2\% CO_2$ in air

9.2 10.8 11.8 12.4 13.7 5.4   5.2 4.4   4.5 4.8   10.6   4.4 5.0   5.0 5.4 3.4 4.8   5.4 5.4 5.8 5.4 6.2
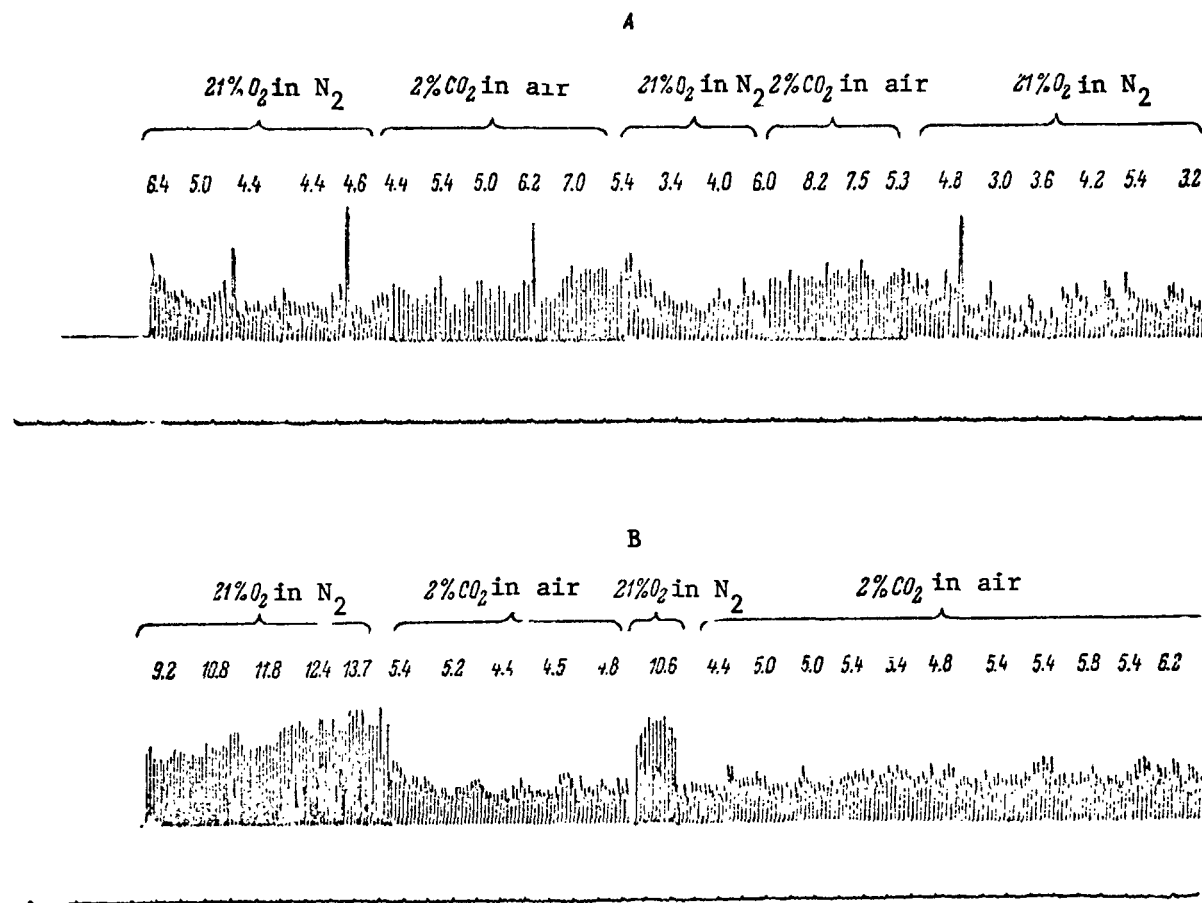
Figure 36. Spirograms of man, obtained during the breathing of air and of a mixture containing 2% CO_2 with correct (A) and incorrect (B) identification of the mixtures by the test subjects. In the first experiment, the respiratory response to the hypercapnic mixture is normal; the mixture is usually avoided by the test subjects. During the second experiment, the subject erroneously thought that the conventional air was the differentiated mixture which caused strong hyperventialtion, which was avoided by the subject. The other notations are the same as in Figure 8.

in the hypoxic medium, not being able to get out of the danger zone quickly enough. Other individuals, on the contrary, had quick and exact reactions. After one or two excursions into the differentiated zone, they chose the undifferentiated end of the chamber, where they remained until the end of the experiment.

Man's ability to distinguish respiratory mixtures is no less variable. Thus, two subjects in only *five minutes of inhalation* distinguished, with no trouble at all, mixtures with comparatively small changes in composition (15% O_2 in nitrogen, or 2% CO_2 in air) from air. The majority of the subjects displayed /121 no regular preference for them. These people served as a standard of man's ability to distinguish respiratory mixtures. On the other hand, there were cases (although they were rare) when the subjects chose mixtures for breathing which caused severe hypoxic or hypercapnic shifts — for example, 7% O_2 in nitrogen or 5% CO_2.

This is a very interesting question. It is not connected with any kind of physiological characteristics of dissimilar responses to altered respiratory environments (Sergeyev, 1935; Kulik, 1967).

From all of our subjects (about 70 people) 5 were selected who expressed the most negative response to breathing hypoxic mixtures, and 5 who, just the opposite, had the most trouble distinguishing these mixtures.

It turned out that the greatest ability to distinguish these mixtures was shown by those with the most regular and comparatively infrequent respiration. Table 3 shows that most of them had reacted to mixtures with 12% O_2 with notably increased pulmonary ventilation, while the subjects who had difficulty distinguishing the hypoxic mixtures had not yet given any ventilator response to them. More severely hypoxic mixtures (9 - 7% O_2) caused more increase of VRM in the "good distinguishers" than in the "poor distinguishers".

It would seem that the respiratory response in people who distinguish hypoxic mixtures easily is more favorable for compensating the oxygen deficiency

TABLE 3

RESPONSES TO A MIXTURE CONTAINING 12% O_2 BY SUBJECTS HAVING VARIOUS ABILITY TO DIFFERENTIATE HYPOXIC MEDIA

| | Index changes, in % of background (21% O_2) | | |
	Choice index (S_t)	VRM	Oxygen saturation of the blood
Mixture distinction:			
Good	-60 ± 14	$+11 \pm 5$	-11 ± 2
Poor	0 ± 20	-6 ± 7	-6 ± 1
Difference between groups	$+60$	-17	$+5$
p	0.1	0.05	0.05

in the medium. However, the lowered oxygenation of the blood under the influence of hypoxic mixtures in this group is not less, but even somewhat more than in the subjects who do not distinguish such mixtures well. A similar discrepancy exists between strong ventilator response and relatively significant impairment of the oxygen regime, and, consequently, also a more intensive hemoreceptor hypoxic im- /122 pulse. Perhaps this is one of the reasons for the sensitivity of some people to a lowered oxygen content in the respiratory environment.

As has been stated, most of the subjects did not distinguish pure oxygen from air, or they reacted negatively to this gas. More rarely, the subjects preferred to breathe the oxygen.

We were able to record that the original pulse rate of most of the subjects who reacted negatively to the oxygen was lower. In oxygen breathing their pulse reduction was less than that in those who reacted positively to the oxygen. Regarding the connection between pulse and oxygen consumption (Margaria, 1965), such a difference in the rate of heart contractions indicates that the hyper-oxic medium is preferred by people with a higher gaseous exchange, and therefore increased oxygen demand.

We did not detect any kind of connection between the ability of individuals to distinguish hypoxic mixtures and their attitude toward pure oxygen.

We shall now dwell on individual characteristics of subjects by their various reactions to hypercapnic mixtures. Differences in gas preference were expressed mainly in relation to mixtures with 3% CO_2 content. The majority of those who easily distinguished an admixture of carbon dioxide had relatively infrequent repiration. They reacted to the hypercapnic mixtures with increased frequency and less depth of breathing. In breathing a mixture with 3% CO_2 concentration, this group also had more of a decrease in pulse rate. Those who did not distinguish or even preferred this mixture of "pure" air had a faster respiratory rhythm. This agrees with what has been indicated by clinical physicians (Burrows et al., 1966) that obstructive lung diseases are characterized by frequent shallow breathing and also by CO_2 being held back in the organism. This is evidently the result of lowered sensitivity to this agent.

Evidently man's ability to distinguish hypoxic media has something in common with his ability to recognize hypercapnic media. Three of the subjects were among those who most sensitively reacted to mixtures with lowered oxygen content and to mixtures with lowered carbon dioxide concentration. However, one of the subjects had difficulty distinguishing both. Such a parallelism does not appear to be accurate. For example, other subjects easily distinguished hypercapnic mixtures, but had difficulty with hypoxic.

The above mentioned characteristics of the physiological functions of those variously distinguishing the hypoxic and hypercapnic mixtures did not always reach a statistically significant level. No kind of regular difference was rec- /123 ognized between these groups according to such things as sex, age (true, all our subjects generally were from one age group), and vital lung capacity.

We must note that the unusual abilities of individuals to distinguish such mixtures are connected not only with characteristics of respiration regulation in these people. They are also related to some characteristics of their higher nervous activity, in the sense of more or less sensitivity to signaling from the internal medium ("vague feelings").

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In the experiments of Gandel'sman which we have mentioned, it was stressed repeatedly that trained athletes possess the ability to differentiate their own hypoxemic shifts exceptionally accurately. We are inclined to support this fact: all five of the subjects who distinguished the hypoxic mixtures most easily were consistently involved in sports. In the group which had difficulty distinguishing these mixtures, only one had athletic training.

But how can we understand the fact that in people who easily differentiate hypoxic respiratory media, the latter cause the most significant lowering of oxygen saturation of the blood? Evidently, resistance to oxygen starvation is not necessarily associated with maintaining a high level of oxygen in the blood. When it is a question of adapting to hypoxia (be it breathing an hypoxic mixture or heavy work) we are primarily talking about economically utilizing oxygen. This was demonstrated not long ago in the research of A.A. Artynyuk (1968). In particular, highly trained athletes under muscular load had a reduction of oxygen in the blood that was not less, but even more, than untrained people. It is possible just this heightened hypoxemic shift also allows man to better "feel deeply" the oxygen lack and more quickly adapt to it.

And from this follows the assumption that man's ability to accurately perceive a lack of oxygen can be one of the criteria of his high resistance to hypoxia.

Age Features of Gas Preference

To study the relationships of response to various respiratory environments with age, the experiments were conducted on three groups of white rats:

    (1) young (1 month);
    (2) mature (5 months);
    (3) old (about 1 1/2 years).

There were about 20 animals in each group.

Figure 37 shows hypoxic, hyperoxic, and hypercapnic gas preference of rats /124 of various ages. Negative response to a mixture with lowered (10%) oxygen

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content was already present in the young animals. This agrees with most researchers, who think that even newborns have completely developed chemoreceptor responses to hypoxemia (Chapter V).

With age, the animals' avoidance of the hypoxic medium becomes somewhat more strongly expressed. Old animals showed the greatest negative response to such a medium. This fact can be connected with the lowered resistance and great sensitivity of the organism to hypoxia which was found in aged people (Lawyer, 1963). A.Z. Kolchinskaya (1963, 1964) noted in people over 80, even under ordinary circumstances, the appearance of oxygen insufficiency, which increased (shortness of breath, sensation of not enough air) when in the mountains at even low altitudes (2,000 meters). N.N. Sirotinin (1966) also thinks that oxygen starvation develops with age. This plays an important role in the origin of early signs of aging. Such senile hypoxia seems to be mostly the result of lowered diffusion ability of the alveolar-arterial membrane (Yadzu, 1965). It also results from inadequate alveolar ventilation because of increased physiological dead space in connection with the tissue oxidation-reduction processes (Seredenko, 1963).   /125

This factor can be connected with the weakly positive response we found in old rats to an hyperoxic environment. This confirms the idea of N.N. Sirotinin that a supplementary oxygen supply is useful in extreme old age. Middle-aged rats mostly responded negatively to the hyperoxic mixture.

Thus, unequal gas preference for mixtures with decreased and increased oxygen content in animals of various ages is evidently connected with the changes which the oxygen regime undergoes in ontogenesis.

Negative response to a hypercapnic medium seems to be inherent in rats of all ages, including the young. This supports data in the literature about the low threshold of hypercapnic respiratory responses in young animals (Yu. Ivanov, 1966), and the sensitivity of arterial chemoreceptors to carbonic acid which is characteristic of even newborns (Purves, 1966). At maturity, negative response to a hypercapnic mixture had a tendency to decrease a little. In old rats it
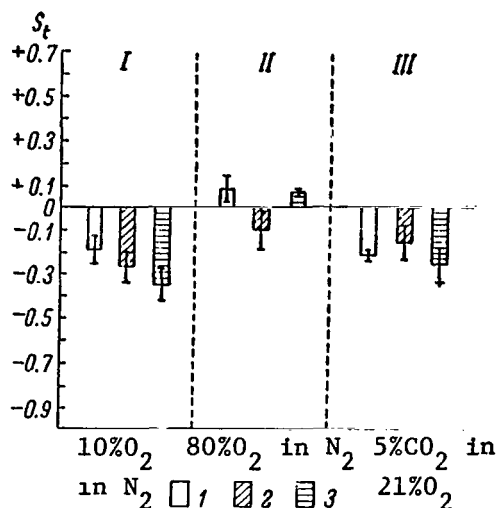
Figure 37. Hypoxic (I), hyperoxic, (II), and hypercapnic (III) gas preference of young (1), mature (2), and old (3) rats. Average data from 20 animals. Vertically – choice index for the differentiated zone (S_t).

again increased slightly. Although these differences are not statistically reliable, they seem to contradict reports of a high threshold of ventilator responses to carbon dioxide admixtures in old animals (Yu. Ivanov, 1966). To explain this question it will probably be necessary to study the oxygen pressure of the alveoli, the blood and the tissues at various ages.

EFFECTS OF EXPOSURE TO A CHANGED
RESPIRATORY ENVIRONMENT AND
ADAPTATION TO IT

From the data cited, it would seem that gas preference to a certain degree reflects the demands made by an organism on the respiratory environment — in particular, on the partial pressure of oxygen.

In his research, Hall (1966) discovered a correlation between the ability of several animals to extract oxygen from the atmosphere and a positive oxyhemoglobin dissociation curve in their blood. The smaller rodents cannot absorb oxygen when it has such a low partial pressure, as can the larger ones. This feature was also confirmed in our experiments. As was shown in Chapter II, negative responses in mice to an hypoxic medium developed at lower degrees of decreased oxygen content in the differentiated zone of the gas gradient chamber than in rats. /12

At the same time, gas preference characteristics in animals and man reflect the adaptability of the organism to the normal content of a respiratory medium that is usual for lower layers of the atmosphere. From this point of view, an organism adapted to an unusual gas medium must also show an altered gas preference.

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Adaptability to altered atmospheric composition can be natural to species living in high-mountain regions or in a medium more or less isolated from the surrounding air, as in deep burrows. It is also known that an organism can acclimatize to an unusual gas composition of the environment during lengthy exposure.

We studied experimentally both natural and acquired "adjustment" of an organism to one or other compositions of the respiratory environment.

Natural Environment and Gas Preference of Some Rodents

As our basic research was conducted on laboratory rodents, it seemed important to set up experiments with those rodents which naturally live in an altered respiratory environment. This group includes animals which inhabit deep burrows where there can be a considerable accumulation of carbon dioxide and decreased oxygen content.

We carried out this work together with A.I. Shcheglova. The research was conducted on species of desert rats, living in burrows. They were extracted at various depths. We studied the giant (*Rhombomys opimus* Licht.), meridian (*Meriones meridianus* Pall.), and crested (*Meriones tamariscinus* Pall.) sand rats; and also the laminated-tooth rat (*Nesokia indica* Gray). Laboratory white rats (*Rattus norvegicus* Berk.) were used as a comparison. Each species was represented in the experiments by 10 - 11 specimens that were 2 - 3 months old.

We studied the animals' responses to the following gas mixtures: 10 and 80% O_2 in nitrogen and 5% CO_2 in nitrogen with a normal oxygen content. The animals were exposed twice to experiments using each of these mixtures. Table 4 shows the data which characterized species differences in the rodents' responses to hypoxic, hyperoxic, and hypercapnic media.

The white rat displayed a severe negative response to the hypoxic medium. The meridian sand rat also responded negatively to oxygen deficiency. There was no response to the hypoxic gas mixture from the crested sand rat or the

laminated-tooth rat. A positive (statistically significant) response to this
medium was even displayed by the great sand rat.

The medium with excess oxygen content caused an insignificant tendency toward positive response in the meridian sand rat and the white rat. At the same time, the great and crested sand rats, as well as the laminated-tooth rat, had practically no response to the hyperoxic medium.

TABLE 4

CHOICE INDEX OF GAS MIXTURES FOR VARIOUS SPECIES OF RODENTS

Species	No. of rats	$10\% \ O_2$ in N_2		$80\% \ O_2$ in N_2		$5\% \ CO_2 + 21\% \ O_2$ in N_2	
		$S_i \pm m$	p	$S_i \pm m$	p	$S_i \pm m$	p
Giant sand rat	11	$+0.17 \pm 0.08$	0.05	0	—	$-0.05 \pm \pm 0.08$	> 0.5
Crested sand rat	10	$+0.18 \pm 0.21$	0.4	$+0.02 \pm 0.23$	> 0.5	$-0.01 \pm \pm 0.12$	> 0.5
Meridian sand rat	10	-0.28 ± 0.09	0.01	$+0.14 \pm 0.09$	0.2	$-0.37 \pm \pm 0.08$	< 0.001
Laminated-tooth rat	10	-0.02 ± 0.17	> 0.5	0	—	$-0.05 \pm \pm 0.06$	> 0.5
White rat	10	-0.55 ± 0.11	< 0.001	$+0.18 \pm 0.14$	0.2	$-0.24 \pm \pm 0.10$	0.05

The white rat and the meridian sand rat displayed a quite clear negative response to the medium with increased carbon dioxide content. The rest of the experimental species — the great and crested sand rats and the laminated-tooth rat — displayed no significant response to its admixture.

The gas preference characteristics of the rodents we studied conform very well with the ecological features of these animals. Spending a considerable portion of their lives in burrows, they live in a peculiar gas regime. The greater or lesser stability of this regime depends on the general architecture of the burrows, the depth of their entrances and nesting chambers. It also

depends on structure, aeration and degree of moisture in the soil. We must add that during great heat or cold rodents often plug up their holes from inside with soil and grass. This diminishes the already poor ventilation (Kucheruk, 1960). Generally, of course, the deeper the burrows are located and the denser the soil in which they are built, the weaker the convection of air in them. Compared with atmospheric air, this air may have a little less oxygen and much more carbon dioxide. It is known that oxygen penetrates into the soil more easily than /128 carbon dioxide is liberated from the soil. The quantity of carbon dioxide in the soil increases with depth (Gilyarov, 1949). About 3% CO_2 is found in the air of the soil, and at a depth of 4m, even up to 8% (Doyarenko, 1915; Lyundegord, 1937). In the sandy soils where desert rodents construct their burrows, the carbon dioxide content at a depth of only 15 cm is 0.25%, and at a depth of 30 cm — 0.31%. This is 10 times greater than its usual quantity in the atmosphere (Lyundergord, 1937). Thus, in proportion to depth below the surface, soil air is characterized by an increased hypoxic and at the same time hypercapnic regime, which ordinarily affects hot climates. Various animals react to these conditions in various ways; it depends on their ecological specialization. Thus, burrowing rodents endure hypoxic conditions better because of the already existing adaptability of their tissues and entire organism to these conditions (Slonim, 1962).

There are data in the literature (Hall, 1966) that rodents which normally live in burrows (or at high altitudes) where partial pressure of oxygen might be reduced have a naturally lower saturation pressure of oxyhemoglobin. These animals can consume oxygen when there is a lower content in it in the atmosphere. The gas preference characteristics of the burrowing rodents we have cited serve to support this.

Of all the species we studied, the crested and, in particular, the great sand rat spend a considerable part of their lives in very deep burrows (up to 3 m). In connection with what has been noted above, it can be assumed that these rodents are adapted to enduring condtions where there is an oxygen deficiency and excess carbon dioxide. Our experiments indicated exactly this. The laminated-tooth rat, similar in these reactions to the previously mentioned sand rats, does not live in deep burrows, but builds them in dense, rarely moistened and poorly ventilated soils.

The meridian sand rat seems to be quite sensitive to insufficient oxygen and increased carbon dioxide concentration. He lives in simply-built burrows with entrances located on the surface. The air in these burrows is similar to the ordinary atmosphere. The latter seems to be the normal medium also for the white rat, which also reacts negatively to a worsening gas composition in the air to which it is not accustomed.

The data obtained confirm that gas preference is closely connected with adaptability to a certain usual composition of the atmosphere.

Influence of Artificial Adaptation to Hypoxia and Hyperoxia on Animals' Gas Preference

As we know, a prolonged period in an environment with lowered partial pressure of oxygen leads to a whole series of adaptive shifts in the respiratory function and allied systems. An increased level of pulmonary ventilation is established (Knowles, 1959; Davidov, 1966, and many others), compensatory reorganization of hemodynamics occurs (Weidman, et al., 1965) especially in the brain's blood supply (Diemer and Henn, 1965; Voytkevich, 1966), erythropoiesis is intensified, and the oxygen capacity of the blood increases (Voitkevich, 1963, Siri et al., 1966; and many others). The function of the hypophysis-adrenalin system is stimulated (Marks, et al., 1965), etc. There are changes at the tissue and even the molecular levels of biochemical processes (Barbashova, 1960, et al.). As a result, an organism's resistance to oxygen starvation is considerably increased.

First of all we had to find out how gas preference changes as a result of adaptation to a hypoxic medium and what the probable physical mechanism of such changes are (Breslav, 1967). The work was conducted on white rats. At first we studied the gas preference of a group of 20 animals in relation to mixtures with altered oxygen and carbon dioxide content. Then this group was exposed to hypoxic adaptations. For a month, the animals were exposed every day for 12 hours in a large chamber filled with a mixture of 10% O_2 and 90% N_2 at atmospheric pressure. This medium corresponds to partial pressure of oxygen at
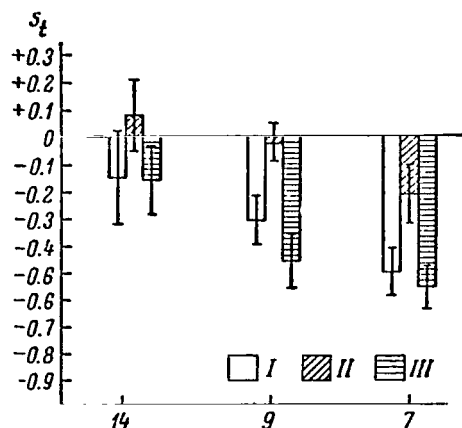
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Figure 38. Hypoxic gas pref-
erence of rats before (I), at
the end (II) and two months
after the completion (III) of
adaptation to a hypoxic en-
vironment. Average data from
10 animals. Horizontally -
percentage of oxygen in the
differentiated zone. The
rest of the legend is the
same as in Figure 37.

an altitude about 6 km above sea level. After
the period of adaptation ended, the gas pref-
erence of the rats was determined once more.
After one month the animals' responses to the
hypoxic medium were determined a third time.

Hypoxic adaptation led to a considerable
decrease in the negative response of rats to
mixtures with a lowered oxygen content. Res-
ponses to a mixture containing 9% O_2 decreased
exceptionally noticeably (Figures 38 and 39).
If the young rats under normal conditions dis-
play a weakly expressed tendency to prefer
oxygen in comparison with ordinary air, then
after hypoxic adaptation they were inclined
to avoid the hyperoxic medium. This, along
with a weakened response to hypoxia, indicates
a change in gas preference toward a lower
oxygen content in the atmosphere.

Negative response of rats toward hypercapnic mixtures increased after
adaptation to an oxygen-poor medium. Their average choice index of a mixture
containing 9% CO_2 changed from -0.38 to -0.72. There is evidence in the liter-
ature of increased sensitivity to carbon dioxide as a result of prolonged exis-   /130
tence under hypoxic conditions (Archibald, 1964; Biget et al., 1965).

A month after the end of hypoxic adaptation, negative responses of rats
to mixtures with inadequate oxygen content not only were reduced, but even ex-
ceeded the original level. This was studied by Tribukait (1963) in rats ex-
posed for a long time at high altitudes. Forty days after returning to sea
level, the animals displayed a reverse response to hypoxic adaptation — an
erratic decrease of the oxygen content of the blood. In this phase it must be
supposed that sensitivity to oxygen starvation would be increased. This was
shown in our experiments in the form of pronounced avoidance of the hypoxic
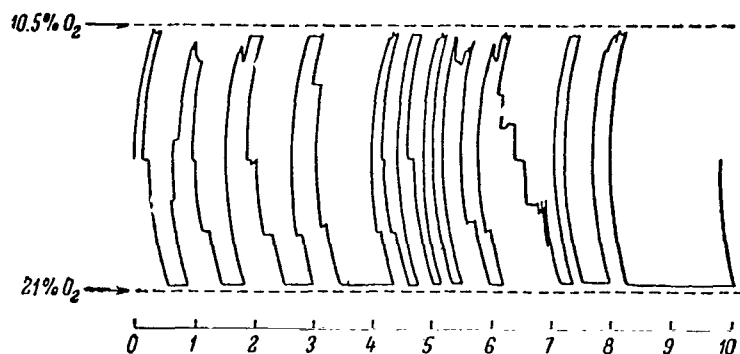
Figure 39. Kymogram of the movements of a rat in a hypoxic
gradient (from 29 to 10% O$_2$) after adaptation to a medium
with 10.5% oxygen content. Avoidance of the hypoxic zone
is weakly expressed (compare with Figure 6, same legend.).

mixtures by the experimental rats.

Summarizing these data, we can conclude that adaptation to an oxygen-poor
atmosphere causes temporary changes of response in relation to various gas
media. In particular, gas preference seemed to be shifted toward lower oxygen
concentrations. Thus, it was possible to observe an adjustment to an altered
gas medium not only in wild species of rodents resulting from their ecological
specialization, but also to reproduce it artificially by means of lengthy exposure
of laboratory animals to an atmosphere of corresponding composition.

If hypoxic acclimatization leads to the organism's adjusting to reduced
partial pressure of oxygen in a medium, then adaptation to a hyperoxic atmos-
phere probably would cause the opposite effect with corresponding change of
gas preference in animals.

To verify this assumption, we exposed rats intermittently (12 hours every /131
day for a month) to a gas mixture containing 75% O$_2$ and 25% N$_2$. The series of
experiments did not differ from those described above with the hypoxic acclima-
tization of rats.

On the basis of data in the literature (Becker-Freuseng and Clamann, 1942;
Ohlsson, 1948; Lazarev, 1951; Mullinax and Beischer, 1958; Balakhovskiy et al.,
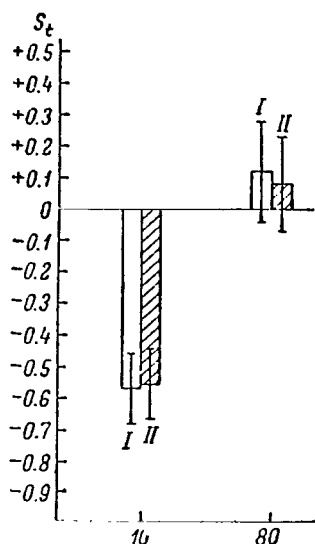
Figure 40. Hypoxic and hyperoxic gas preference of rats before (I) and at the end of (II) adaptation to a hyperoxic environment. The legend is the same as in Figure 38.

1962), 75% concentration of oxygen can be considered as close to the safe maximum. In any case, such a medium does not cause oxygen poisoning in animals exposed for many days, although accurate limits of more or less successful adaptability to hyperoxic medium have not as yet been definitely established (Zhironkin and others, 1965; Troshikhin, 1966). Besides, it must be taken into account that an organism adapts more easily to the intermittent effect of hyperoxia than to a constant effect (Boycott and Oakley, 1932).

As is shown in the results of determining the hypoxic and hyperoxic gas preference in rats before and after their exposure to a medium with increased oxygen content, negative response of animals to a mixture containing 10% O_2 did not undergo any changes. Adaptation to a hyperoxic atmosphere hardly influenced even the tendency of the experimental rats toward a weakly expressed positive ·reponse to a medium with an over-concentration of oxygen (Figure 40).

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Consequently, adaptation to an oxygen-enriched gas medium did not cause in the animals any kind of significant shift (judging by their gas preference) of "adjustment" to a specific oxygen content in the atmosphere, although an hypoxic medium causes such a shift. Evidently, a lack of oxygen, as opposed to its excess, has a specific effect. Hypoxemia is really one of the inseperable components of muscular activity ("motor hypoxia", as it is expressed by A.B. Gandel'sman), and adaptation to this factor is customary for the organism. Not without reason, adaptation to hypoxia improves efficiency, and physical training in its turn makes it easier to adapt to an oxygen-poor atmosphere (Hurtado et al., 1956, cited by: Schreuder, 1966; Barbashova, 1960; Letunov, 1965; Salatsinskaya, 1967). The hyperoxic medium, although it also causes adaptive responses (see Chapter II), is a physiologically inadequate factor

and therefore does not have the ability to change an organism's "adjustment" to a specific oxygen regime.

Exposure to a Rarified Atmosphere and Gas Preference in Man

In man we had to find out how gas preference changes during a period in an altered gas medium. In particular, it was necessary to study active choice responses to mixtures with rapid switching to ordinary atmosphere, as well as during extended periods.

The first part of our problem was solved by "ascents" in an altitude chamber. We used a Model PBK-53 altitude chamber, suitably redone. A special compensator valve permitted the subjects to breathe the gas mixtures through spirographic equipment mounted on the outside (described in Chapter I). Resistance was fixed, and it did not depend on the degree of air vacuum inside the chamber.

The gas preference of the subjects was studied at "altitudes" from 0 to 6.7 thousand meters. First an "ascent" was made to a certain pressure. Then the experiment was conducted according to the usual program. The respiration time for breathing each of the offered mixtures was 15 minutes. At the end /133 there was a "descent". In each experiment air (21% O_2) was compared to a mixture with an increased oxygen content (from 30 to 98%).

We found that man clearly distinguishes these hyperoxic mixtures, preferring them to ordinary air if the "altitude" in the chamber reaches 3 – 4 thousand meters:

"Altitude" (in thous. m.)	Percent of subjects choosing mixtures with increased con- tent of O_2
0	33
2.8	43
4.5	88
6.7	100

Under these conditions, breathing mixtures with an increased oxygen content not only raised oxygenation of the blood, but also led to lowered pulmonary ventilation. This indicated an oxygen deficiency (Haldane and Priestley, 1935; Dembeau, 1957; Malova, 1962; et al)

It is known that the higher the oxygen concentration in a respiratory mixture, the greater the atmospheric pressure at which such a mixture can maintain adequate P_{O_2} in the pulmonary avleoli (Carlyle, 1963; and others). In this case the "physiological equivalent of altitude" is revealed in the positive reponses of the subjects to hyperoxic mixtures on reaching certain "altitudes". An analogous phenomenon was noted by Finkelstein et al (1965): in the pressure chamber at high "altitudes", pure oxygen caused a feeling of decreased respiratory effort in man.

To explain how active choice of respiratory mixtures changes in the process of adapting to an unusual atmosphere, we tried to find out what shifts of gas preference man makes during periods in the mountains.

Living in a high-mountain climate is an effective means of acclimatizing the human organism to hypoxia (Agadjanyan et al., 1967; and many others). The basic factor here is, of course, the lowered partial pressure of oxygen. An important factor is also the intensive muscle load which accompanies a mountain climb. This considerably increases the oxygen demand of the tissues. By increasing "external" hypoxia, muscular activity increases the efficiency of adaptation to an oxygen deficiency (Salatsinskaya, 1967, et al.).

Our experiments in the mountains were conducted with people who had various (in general, not much) mountain climbing experience. First we determined the subjects' responses to respiratory mixtures with various oxygen and carbon dioxide content. This was done under laboratory conditions at sea level by /134 the usual method. Then they moved to the region of the mountain camp at Uzon-Kol (Western Caucausus). They lived here at an altitude 2.2 km above sea level for a month and underwent intensive mountaineering training, including climbs to 4.2 km. During this period in the mountains, the subjects spent the next to

Figure 41. Changes in human responses to an hypoxic mixture (P_{O_2} = 80 mm Hg) under the influence of a period in the mountains. Data from 10 subjects. The legend is the same as in Figure 7. (mts. = mountains)

the last week at an altitude of 3 km above sea level.

Upon their arrival in the mountains, and also several times during their stay at high altitudes, the subjects were repeatedly tested for their response to gas mixtures. These same experiments were conducted again after their return to low level. We must point out that in the mountains mixtures were used with a somewhat lowered composition in comparison with those used at low levels. This was done to maintain the same partial pressure of the differentiated gases allowing for decreased general barometric pressure of 589 mm Hg at an altitude of 2.2. km (instead of 10.5% O_2, the mixture contained 13.6% O_2; 7% concentration of O_2 was replaced by 9.1%; the hypercapnic mixture in the mountains contained not 5, but 6.5% CO_2).

As a result of the influence of the lowered partial pressure of oxygen, all the subjects in the mountains developed decreased oxygenation of arterial blood, increased pulse rate and increased VRM. In the first few days some complained of headache and fatigue.

With this background, breathing hypoxic mixtures caused increased ventilator response and an even greater decrease in oxygenation of the blood (Figure 41). Analogous facts have been noted by a number of researchers (Lefrancois et al., 1966; and others). Man's ability to distinguish mixtures with a lowered oxygen content increased; negative response to such mixtures was much more constant than under low-level conditions. When the oxygen content in a closed system of return respiration was lowered gradually, the subjects noted the change in their own feelings ("it's harder to breathe", "not enough air",
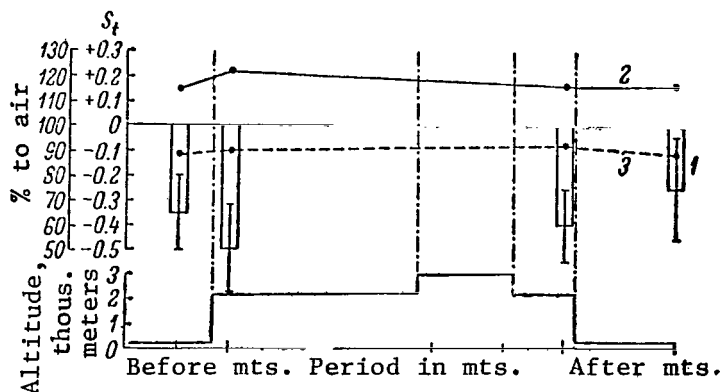
Figure 42. Changes in human responses to pure oxygen under the influence of a period in the mountains. Data from 10 subjects. The legend is the same as in Figure 7.

etc.) earlier and at a smaller decrease of the percentage of oxygen in the medium than at sea level. The onset of severe hypoxia, which forced the experiment to be ended, also occurred earlier. These experiments confirmed that the chemoreceptor stimulus of respiration, caused by an oxygen deficiency, is retained completely by people who have arrived at a high-altitude zone from a low level (Lefrancois et al., 1966).

On the other hand, negative response to pure oxygen disappeared in the mountains (Figure 42). Breathing oxygen caused a more noticeable increase of oxygenation of the blood in the subjects than it did at sea level. These characteristics of response to oxygen were still more strongly expressed when the subjects arrived at an altitude of 3,000 meters. Here inhalation of oxygen was accompanied by a significant decrease of VRM, and in the majority of cases by a positive response ("easier" or "milder" to breathe in comparison with air). These data agree basically with the results obtained in the altitude chamber experiments.

It was shown above that animals exposed to a hypoxic medium develop an increased sensitivity to carbon dioxide. An analogous phenomenon can also be noted in people: the subjects distinguished the hypercapnic mixture (P_{CO_2} was 38 mm Hg) more clearly in the mountains than at low levels; corresponding choice /136 indexes were -0.56 ± 0.12 and -0.45 ± 0.11. Ventilator response to hypercapnia also increased, which agrees with data presented by other authors (Chiodi, 1957; Michel and Milledge, 1963; Akhmedov et al, 1968).

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By the end of the month-long period in the mountains, the subjects had developed signs of high-altitude acclimatization. They felt better, the level of oxygenation of the blood increased, tachycardia disappeared.

In this period, responses to breathing various gas mixtures also changed. Negative response to a moderate hypoxic medium decreased somewhat (Figure 41), but response to pure oxygen again became weakly negative (Figure 42). This can be considered as a sign of the restoration of a more or less normal oxygen regime.

Thus, a period in the mountains is accompanied in man by a natural change in respiratory responses and preference for various mixtures. This is connected, on one hand, with a specific degree of oxygen insufficiency in an organism, and, on the other hand, with developing adaptation to the hypoxic medium.

After the subjects returned to lower levels, their responses to mixtures with an altered oxygen content returned to approximately what they were originally. We did not succeed in observing aftereffects of adaptation to hypoxia in man; these were noted in animal experiments. This is probably explained by the relatively longer interval (6-7 days) between the subjects' descent from the mountains and the beginning of the experiment under low-level conditions. By this time adaptation could have been lost to a significant degree (Alipov, 1969, et al.).

Thus, the dynamics of human gas preference reflect to a specific degree those physiological shifts which develop in the transition to an altered respiratory medium and in the process of adapting to it.

The data discussed in the present work can be considered in two aspects: analyzing the ability to differentiate changes in the composition of inhaled gas mixtures, and analyzing the physiological adequacy of those mixtures.

THE ABILITY TO DISTINGUISH CHANGES IN THE COMPOSITION
OF A GAS MEDIUM

Even a brief survey of "respiratory behavior" of animals on a physiological level shows that the choice of a preferred gas medium — gas preference — is for many organisms an important form of regulating respiration. It is a natural reflex act, resulting from impulses from corresponding chemoreceptors.

In higher animals and man, who live in an atmosphere of almost homogeneous composition, gas preference can be shown only by experimental means. This kind of behavioral response to factors not encountered in the normal medium is already known. As an example, we can use radioactive irradiation. The organism does not have any kind of receptors for direct perception of ionizing radiation. Nevertheless, in experiments on animals, negative responses to radiation, or more accurately to those conditions in which it occurred, have been successfully observed (Garcia et al., 1955; Darenskaya and Pravdin, 1968; and others). Evidently, behavioral responses to radiation are produced on the basis of a combination of internal impulses and the accompanying signals from the surrounding environment. Our research indicates a similar mechanism of gas preference response. The organism is not able to distinguish the composition of a gas medium directly (and in ordinary life it has no need to), but perceives changes in it through shifts which take place in the internal medium. The blue-yellow and other "internal" chemoreceptors evidently serve as sensory apparatus here.

As has been emphasized, verbal signaling is a part of the human response
to changes in the composition of inhaled mixtures. Evidently, in this case
there is the possibility of perfecting the ability to distinguish gas media.
As man perceives changes in the composition of the atmosphere by his own internal
medium, then the better he is able to perceive (more accurately, to transfer to
the verbal level) the interoceptive signals received by the brain, and the sooner
he notices shifts of the gas regime in his own organism. In fact, instructions
about the necessity of recording, i.e., verbally formulating, the onset of a
feeling of weariness accelerates the manifestation of fatigue during muscular
work (Liberman and Trubitsina, 1954). If a man is informed before an experiment
about the signs of hypoxia and hypercapnia, he will be able to evaluate more ac-
curately the shifts of the gas regime which develop in return respiration in a
closed system (Gandel'sman et al., 1966).

Individual characteristics of people in relation to such self-evaluation
are quite diverse. We still have little data for a decisive answer to the
question of man's ability to be trained to distinguish gas mixtures. But in
principle, such training is completely possible. Of course we are talking
about moderate shifts in the composition of an inhaled medium. It must not be
forgotten that in severe degrees of hypoxia and hypercapnia the differentiat-
ing function of the brain is impaired (Brestkin, 1968; et al.). The effect of
this is loss of adquate behavioral responses, which we also noted in animal
experiments.

The practical side of this problem is important. It is sufficient to
point out the problems of safeguarding pilots and cosmonauts from oxygen star-
vation. In domestic and foreign aviation medicine, attention is constantly
being drawn to the dangers with which high-altitude hypoxia is fraught. The
necessity of using oxygen in specific situations is also emphasized. G. Arm-
strong (1954) considered the lack of sensations, quite typical of hypoxia, as
the most important reason for the indifference of some specialists and pilots
themselves to this problem. "In almost all impairments in an organism, nature
gives warning signals in the form of feelings of sickness or other unpleasant-
ness. In altitude sickness, on the contrary, not only can all symptoms

be lacking, but sometimes a feeling of well being is completely maintained ... Therefore, it must be regretted that altitude sickness is not accompanied by illnesses or other unpleasant sensations. If this were so, the health of the flight personnel and the safety of the pilots would profit." (Armstrong, 1954:223).

To these words we must add that it is as if the inadequate subjective signals of hypoxia develop and consolidate in certain cases. A published report   /139 has recommended that man's ability to "feel" ionizing radiation be developed in order to provide a natural system of fatique when there is a hazard [1]. We think that it is easier (and frequently also more important) to improve man's ability to detect those changes in the composition of the respiratory medium which are important for his efficiency, health, and sometimes even his very life.

GAS PREFERENCE AND ADEQUATE RESPIRATORY ENVIRONMENT

Research data lead us to the conclusion that the gas preference of higher animals and man can serve as an indication of the range of changes in the composition of the respiratory environment within which ordinary adaptive mechanisms are sufficiently effective, at least for short periods. Negative responses to breathing specific mixtures are activated when these mechanisms are insufficiently effective and/or excessively strained. As has been noted, in man this kind of response of his own mechanism is similar to the effects of shortness of breath. This can be considered as a negative response to a disparity between the respiration regime and the gas composition of the internal medium.

Studying the active choice response to gas media in animals and man, under altered atmosphere conditions for prolonged periods or temporarily, has led us to the conclusion that gas preference is connected with "tuning" of physiological functions to a certain composition of the respiratory environment This tuning is composed of both inherent (the result of natural selection) and acquired (the result of adaptation) responses.

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In the wide sense, gas preference reflects the relationship between the physiological composition of the organism and adequate limits of the partial pressure of respiratory gases. Following the classification of forms of behavior proposed by A.D. Slonim (1967), the choice of a preferred gas mixture can be defined as "a reflex for the preservation of the internal medium of an organism and the conservation of matter".

Some analogy is apparent between the choice of respiratory media and the choice of various forms of food and drink mixtures. An organism reacts differently to food in general depending on its satisfied or starving condition (Stroganov, 1929; and others). When a diet is altered, positive responses to deficient substances increase and are decreased in relation to excessively introduced substances (Savich, 1913; Breslav, 1951; et al). I. P. Pavlov (1923) called the food center the acceptance regulator of substances necessary /140 for vital chemism. The intake of water and salt is delicately regulated (Cassil', 1964; Beck et al., 1965).

B.N. Chernigovskiy writes about active choice responses: "Signaling, which comes from interoceptors, is important not only for regulating system functions of an organism, but also is capable of effectively influencing the behavior of the animal ... The lack of one or other ingredient causes complex behavioral responses in the animal. ... These data," Chernigovskiy notes further, "indicate that the higher sections of the central nervous system (without them, of course, any kind of complex behavioral acts are impossible) are not only necessary in a stabilized internal medium for active adaptation of an organism to the surrounding medium. In higher animals they themselves become one of the factors maintaining homeostasis." (1960:576).

We have already expressed the thought that in some cases the optimum environment for an organism can be not his usual atmosphere, but a gas mixture of another composition. As a matter of fact, in heavy muscular work, accompanied by expressed hypoxemia, the physiologically adequate medium is probably one enriched with oxygen. Demands on the respiratory environment change also when there is insufficient oxygen and excess carbon dioxide from other

causes — in particular, gas preference shifts in the mountains or on a background of hypercapnia.

Evaluating various formulae for an artificial room atmosphere, V.B. Malkin (1968) indicated the possibility of using an "active" gas medium which ought to tone up the organism, create the necessary functional load, especially necessary under conditions of hypodynamia and weightlessness during space flight. The author assumes that such factors as periodic deficiency or excess of oxygen and increased carbon dioxide concentration will be used. In his opinion, "stimulating" and "inhibiting" atmospheres could be alternated to maintain the necessary rhythm of work and rest.

We suggest that the gas preference method can also be used in solving these problems. A study of positive and negative active choice responses to the vast spectrum of gas mixtures shows approximately what respiratory medium composition is most suitable for a given organism in specific conditions of its vital activity. This helps in choosing optimum variants and safe deviations in the composition of an artificial atmosphere for men working in high-altitude or space flights, underwater or underground descents, etc. This might also prove useful as the physiological basis for using various respiratory mixtures for medical purposes.

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1. Science et Vie, No. 539, 1962, p. 46.

2. Aver'yanov, A.G., G.Y. Vladimirov, Z.E. Grigor'yev, B.D. Kravchinskiy, M.L. Rylova, and P.N. Smukhin. The Influence on the Human Organism of a Prolonged Period in a Hermetically Sealed Room with No Ventilation under Various Meteorological Conditions. Fiziologicheskiy zhurnal SSSR, Vol. 19, No. 6, 1935, pp. 1207-1228.

3. Agadzhanyan, N.A., A.S. Barer, G.A. Golov, G.A. Davydov, I.I. Dedenko, G.P. Doronin, V.B. Zubavin, A.G. Kuznetsov, V.V. Parin, A.S. Pankova, Ye.A. Sokol, Ye.P. Tikhomirov. The Influence of Mountain Acclimatization on Human Ability to Endure Prolonged Active Acceleration and Thermal Load. Ucheniy zapiski, Kabardino-Balka Universiteta, Vol. 33, 1967, pp. 159-160.

4. Ayrapet'yants, E.Sh., and A.V. Pogrebkova. Respiration Analyzer. Zhurnal vysshikh nervnikh deyatel'nostey, Vol. 13, No. 2, 1963, pp. 218-227.

5. Aleksandrov, A.F., and P.I. Yegorov. Altered Gaseous Exchange During Short Periods in a Rarified Atmosphere. In: Kislorodnoye golodaniye i bor'ba s nim (Oxygen Starvation and its Prevention), Leningrad, 1947, pp. 20-30.

6. Alipov, D.A. O vosmozhnostyakh ispol'sovaniya sredogor'ya v povyshenii effektivnosti sportivony trenirovki (The Possibility of Using the Central Mountains for Athletic Training). Author's abstract for dissertation, Frunze, 1969.

7. Altukhov, G.V., and B.V. Malkin. A Study of the Influence of Severe Oxygen Starvation on Heart Activity. Klinicheskaya Meditsina, Vol. 30, No. 10, 1952, pp. 45-51.

8. Al'birskiy, P.M. Odnostromost' i oshibochnost' sovremennogo fiziologischeskogo ucheniya o znachenii produktov obmena (Prejudice and Inaccuracy in Recent Physiological Studies of the Signficance of Exchange Products), Petrograd, 1918.

9, Ananov, S. O terapevticheskom primenenii vdykhayemogo kisloroda (The Therapeutic Use of Inhaled Oxygen). Dissertation, St. Petersburg, 1873.

10. Anisimov, Ye.A. Ispolzovaniye vdykhaniya karbogena i vosdukha, obogashchennogo kislorodom, dlya uskoreniya vosstanovitel'nykh protessessov u sportsmenov. (The Use of Breathing Carbogen and Air, Enriched with Oxygen, to Accelerate Restoration Processes in Athletes). Materialy X Vsesoyuzn. nauchn. konfer. po fiziologii, morfologii, biomekhanike, i biokhimii myshechnoy deyatel'nosti (Data from the 10th All-Union Scientific Conference on the Physiology, Morphology, Biomechanics and Biochemistry of Muscular Activity), Volume 1, Moscow, 1968, p. 16.

11. Anichkov, S.V., and M.L. Belen'kiy. Farmakologiya khimioretseptorov karotidnogo klubochka (Pharmacology of chemoreceptors in the carotid body). Leningrad, 1962.

12. Arakcheyev, A.I. Respiratory insufficiency. Vrachebnoye Delo. Vol. 4, 1967, pp. 59-64.

13. Ardashnikova, L.I. Znacheniye razlichnykhkhemoretseptornykh oblastey v regulyatsii dykhaniya pri nedostatke kisloroda (The Significance of Various Hemoreceptor Regions in Regulating Respiration during an Oxygen Insufficiency) Works of the Institute of Normal and Pathological Physiology, Academy of Medical Sciences, USSR, Vol. 3, 1959, pp. 64-73.

14. —————————. The Participation of Arterial, Venous and Tissue Receptors in the Regulation of External Respiration during Hypoxemia. In: Kislorodnyy rezhimorganisma i yevo regulirovaniye (The Oxygen Regime and its Regulation) Kiev-Kanev, 1965, pp. 15-17.

15. —————————. O mekhanismakh ismenniy oykhaniya i krovoobrashcheniya /143 pri gipoksicheskoy gipoksii. (The Mechanisms of Changes in Respiration and Blood Circulation in Hypoxic Hypoxia). Materialy 3-y konfer. fiziologov Sredney Axii i Kazakhstan (Data from the Third Conference of Physiologists of Central Asia and Kazakhstan). Dushanbe, 1966, pp. 31-33.

16. Ardashnikova, L.I., and L.I. Shik. Mechanism of the Effects of Severe Hypoxemia on Respiration. In: K regulyatsii dikhaniya, krovobrashchen-iya i gasoobmena (Regulation of Respiration, Blood Circulation, and Gaseous Exchange), Moscow, 1948, pp. 25-31.

17. Ardov, M.M. K boprosu o vzaimosvyazi mezhdu raspredeleniyem temperatury, kisloroda i skopleniyem rybi v nekotorykh promyshlovykh rayonakh Barentseva i Norvezhskogo morey (The Relationship between Temperature and Oxygen Distribution and the Accumulation of Fish in Several Commercial Fishing Areas of the Barents and Norwegian Seas). Trudy Polyarnogo N.-issl. inst. morsk. rybnogo khoz. i okeanografii (Transactions of the Polar Scientific-Research Institute of Marine Fishing and Oceanography), Vol. 16, 1964, pp. 251-268.

18. Armstrong, G. Aviation Medicine. Translated from English, Moscow, 1954.

19. Artynyuk, A.A. Gazovyy obmen i oksigenatsiya arterial'noy krovi pri napryazhenooy tsiklicheskoy rabote v svyasi s razlichnoy trenirovannost'yu cheloveka (Gaseous Exchange and Oxygenation of Arterial Blood During Strenuous Cycling in Variously Trained People). Author's abstract for dissertation, Leningrad, 1968.

20. Arkhangel'skaya, N.A., and A.N. Segal'. Regulation of Respiration under Insufficient Oxygen Conditions. Byulleten Eksperimental'noy biologii i meditsini, Vol. 37, No. 1, 1954, pp. 23-26.

21. Akhmedov, K.Yu., R.S. Vinnitskaya, and N.A. Koganova. Responses of the Respiratory Center to CO_2 under High-Altitude Conditions. Fiziolog. zhurn. SSSR, Vol. 54, No. 11, 1968, pp. 1348-1354.

22. Balakhovskiy, I.S. Oksigemometricheskiye issledovaniya pri ostroy gipoksii i sootnosheniye ikh s izmennieniyami bioelektricheskoy aktivnosti mozga (Oxyhemometric Research in Severe Hypoxia and its Relationship with Changes in the Bioelectric Activity of the Brain) Tr. Konf. po oksigemometrii (Transactions of the Conference on Oxyhemometrics), Leningrad, 1952, p. 90.

23. Balakhovskiy, I.S., A.R. Mansurov, and V.I. Yazdovskiy. The Influence of Breathing Pure Oxygen on the Lungs and Heart of White Rats. Byulleten eksperimental'noy biologii i meditsini, Vol. 53, No. 2, 1962, pp. 43-47.

24. Barbashova, Z.I. Akklimatizatsiya k gipoksii i yeye fiziologicheskiye mekhanizmy (Acclimatization to Hyperoxia and its Physiological Mechanisms). Moscow-Leningrad, 1960.

25. Barnatskiy, V.N. Elektroentsefalographicheskoye issledovaniye dinamiki uslovnoreflektornoy deyatel'nosti krolikov posle kratikovremennogo vdykhaniya povyshennykh kontsentratsiy uglekisloty (Electroencephalographic Research in the Dynamics of Conditioned-Reflex Activity of Rabbits after Temporarily Breathing Increased Concentrations of Carbon Dioxide). Tr. konfer. po voprosam elektrofiziologii nernoy sistemy (Transactions of the Conference on Electro-Physiology of the Nervous System), Kiev, 1960, pp. 37-38.

26. Bezuglyy, V.P. Altered Gaseous Exchange in Oxygen Therapy for Hypertonic Illness. In: Fiziologiya i patologiya dykhaniya, oksigenoterapiya i giperoksiya (Physiology and Pathology of Respiration Oxygen-Therapy and Hyperoxia), Kiev, 1958, pp. 350-355.

27. Belen'kiy, M.L. Chemical Sensitivity Mechanism of the Carotid Body Receptors. In: Voprosy farmakologii vegetativnoy nervnoy sistemy (Questions on the Pharmacology of the Vegetative Nervous System), Leningrad, 1952, pp. 51-67.

28. Beller, N.N. The Significance of Interoceptors in Regulating Oxygen Saturation of Arterial Blood. Byulleten eksperimental'noy biologii i meditsini, Vol. 45, No. 3, 1958, pp. 45-47.

29. Beregovkin, A.V., P.V. Buyanov, and V.B. Malkin. Respiration and Gaseous Exchange in Severe Hypoxic Test. In: Aviatsionnaya i Kosmicheskaya meditsina (Aviation and Space Medicine), Moscow, 1963, pp. 72-75.

30. Berkovich, Ye.M. Human Respiration Regime at Rest and Working. Fiziologicheskiy zhurnal, SSSR, Vol. 26, No. 4, 1939, pp. 408-420.

31. Berkovich, Ye.M., and K.I. Shakhnovich. The Influence of Breathing Oxygen on Gaseous and Mineral Exchange in Pulmonary Anoxemia. Byulleten eksperimental'noy biologii i meditsini, Vol. 10, No. 5, 1940, pp. 380-382.

32. Bernshteyn, Ye.A. O napryazhenii kisloroda v tkani mozga pri gipoksii (Oxygen Pressure in Brain Tissues during Hypoxia). Materialy X Vsesoyuzn. nauchn. konfer. po fiziologii, morfologii, biomekhanike i biokhimii myshechnoy deyatel'nosti (Data from the Xth All-Union Scientific Conference on the Physiology, Morphology, Biomechanics and Biochemistry of Muscular Activity), Vol. 1, Moscow, 1968, pp. 56-57.

33. Bershteyn, S.A. Changes in Basic Parameters of Hemodynamics with Insufficient Oxygen in Inhaled Air. Fiziologicheskiy Zhurnal, Academy of Sciences USSR, Vol. 12, No. 5, 1966, pp. 649-654.

34. Boriskin, V.V., P.A. Gul'tyayev, and B.M. Savin. The Possibility of the Development and Prolonged Existence of Biological Subjects in a Helium-Oxygen Atmosphere. In: Aviatsionnaya i kosmicheskaya meditsina (Aviation and Space Medicine), Moscow, 1963, pp. 78-81.

35. Brandgendler, V.S. O vliyanii kisloroda i uglekisloty na vazomotornyye svoystva krovi (The Influence of Oxygen and Carbon Dioxide on the Vasomotor Properties of the Blood). Tr. Timiryazevsk. n.-issl. inst. (Transations of the Timiryazev Scientific Research Institute), Moscow, 1927, pp. 25-34.

36. Brandis, S.A., S.A. Iosel'son, and V.N. Pilovitskaya. Functional Changes in an Organism at Rest and during Work during Many Hours of Breathing Gas Mixtures with a Large Oxygen Content. Fiziologicheskiy zhurnal SSSR, Vol. 46, No. 7, 1960, pp. 801-809.

37. Breslav, I.S. Gasoobmen i natural'nyye uslovnyye pishchevyye refleksy s obonyatel'nogo analizatora (Gaseous Exchange and Natural Conditioned Food Reflexes from an Olfactory Analyzer). Author's abstract for dissertation. Leningrad, 1951.

38. Breslav, I.S. Gasovyy preferendum belykh myshey v usloviyakh gradienta kisloroda i uglekislovo gasa (Gas Preference of White Mice in Oxygen and Carbon Dioxide Gradient Conditions), Doklady AN SSSR, Vol. 150, No. 5, 1963, pp. 1168-1170.

39. ——————. Methods of Studying Gas Preference in Small Animals. Fiziologicheskiy zhurnal SSSR, Vol. 51, No. 5, 1965a, pp. 628-631.

40. ——————. Gas Preference in Animals. In: Slozhnyye formy povedeniya (Complex Behavior Forms), Moscow-Leningrad, 1965b, pp. 197-202.

41. —————— Dynamics and Alterations of Motor Responses in Animals to Various Hypoxic Media. Zhurnal vyshikh nervnikh deyatel'nostyey, Vol. 15, No. 4, 1965c, pp. 677-682.

42. ——————. Active Avoidance of Hypoxic Media by Animals and Man. In: Kislorodnyy rezhim organizma i yevo regulirovaniye (The Oxygen Regime and its Regulation). Kiev , 1966, pp. 299-304.

43. ——————. Gas Preference as an Indication of Adaptation to a Specific Atmospheric Composition. In: Issledovaniya adaptivnogo povedeniya i vyshey nervnoy deyatel'nosti (Studies of Adaptive Behavior and Higher Nervous Activity), Novosibirsk, 1967, pp. 26-28.

44. Breslav, I.S., B.N. Volkov, and V.M. Mityushov. Apparatus for Studying the Influence of Various Gas Mixtures on Human Respiration. Fiziologicheskiy zhurnal SSSR, Vol. 55, No. 1, 1969, pp. 104-108.

45. Breslav, I.S., and A.G. Zhironkin. K voprosu o bzaiumodeystvii korkovykh i reflektorno-gumoral'nykh mekhanizmov v regulyatsii dykhaniya cheloveka (The Interaction of Gray-Matter and Reflector-Humoral Mechanisms in Regulating Human Respiration). Sbornik materialov IV nauch. konfer. fiziologov, biokhimikov i farmakologov Zap. sibirskogo ob'yedineniya (Collection of data from the IVth Scientific Conference of the Western-Siberia Society of Physiologists, Biochemists, and Pharmacologists), Krasnoyarsk, 1969, pp. 41-43.

46. Breslav, I.ᴗ., A.G. Zhironkin, and Ye.N. Salatsinksaya. Active Choice by Animals and Man of Nitrogen-Oxygen and Helium-Oxygen Mixtures. Fiziologicheskiy zhurnal SSSR, Vol. 51, No. 12, 1965, pp. 1501-1506.

47. Breslav, I.S., and A.M. Il'nitskiy. Apparatus for Studying the Influence of a Gas Medium on Experimental Animals. Byulleten izobretatelye, Vol. 24, No. 167013, 1964.

48. Breslav, I.S., and Ye.N. Salatsinskaya. The Influence of a Helium Medium on Responses to Insufficient Oxygen and Excess Carbon Dioxide In: Problemy kosmicheskoy meditsiny (Problems of Space Medicine), Moscow, 1966, pp. 73-74.

49. Breslav, I.S., and Ye.N. Salatsinskaya. Man's Distinction of an Admixture of Carbon Dioxide in Inhaled Air. Fiziologicheskiy zhurnal SSSR, Vol. 53, No. 8, 1967, pp. 957-963.

50 ──────────────────── Human Responses to Hypoxia and Hypercapnia in Breathing Nitrogen- and Helium-Oxygen Mixtures. In: Problemy kosmicheskoy biologii (Problems of Space Biology), Moscow, Vol. 7, 1967, pp. 212-220.

51. ──────────────────. Man's Distinction of Respiratory Mixtures with Decreased and Increased Oxygen Content. Fiziologicheskiy zhurnal SSSR, Vol. 54, No. 7, 1968, pp. 850-855   /145

52. Brestkin, M.P. I.M. Sechenov ── sozdatel' teorii sostava al'veolyarnogo vozdukha (I.M. Sechenov ── Originator of the Theory of the Composition of Alveolar Air). Leningrad, 1952.

53. ──────────. Funktsii organizma v usloviyakh izmennoy gazovoy sredy (Functions of an Organism in Altered Gas Medium Conditions), Leningrad, 1968.

54. Bronshteyn, A.I. Vkus i obonyaniye (Taste and Smell), Moscow-Leningrad, 1950.

55. Bukov, V.A. Participation of the Higher Respiratory Tract in Regulating Breathing and Blood Circulation. Byulletin eksperimental'noy biologii i meditsini, Vol. 11, No. 5, 1941, pp. 543-546.

56. Buteyko, K.P., S.A. Garmash, D.V. Demin, and M.P. Odintsova. The Influence of Voluntary Regulation of Respiration on Some Physiological Functions at High Altitudes. In: Voprosy aviatsionnoy meditsiny (Problems of Aviation Medicine), Moscow, 1966, pp. 94-99.

57. Vacksleyger, G.A. Izmeneniya reflektornoy vozbudimosti dikhatel'nogo tsentra pro povishenii soderzhaniya CO_2 vo vdykharemom vozdukhe (Changes in Reflector Excitability of the Respiratory Center in Increased CO_2 Content in Inhaled Air). Tr. Orenburgsk. otdel. Vsesohuzn. obshch. fiziologov (Transactions of the Orenburg All-Union Society of Physiologists), Vol. 2, 1960, pp. 34-42.

58. ──────────────. The Mechanism of the Effect of Oxygen at Normal Atmospheric Pressure. In: Kislorodnyy rezhim organizma i yevo regulirovaniye (The Oxygen Regime and its Regulation), Kiev-Kanev, 1965, pp. 31-36.

59. Vacksleyger, G.A., I.I. Grechishkin, L.F. Yeremenko, and L.K. Layzon. Nekotoryy reaktsii organizma pri izmenenii gazovogo sostava vdykhayemogo vozdukha. (Some Responses to Altered Gas Composition of Inhaled Air). Materialy 5-y Povolzhskoy konf. fiziologov, biokhimikov i farmakologov (Data from the Fifth Volga Conference of Physiologists, Biochemists and Pharmacologists) Gor'kiy, 1963, pp. 31-33.

60. Vinnikov, Y.A. Istoricheskiy metod i yego rol' v reshenii problem
     evolyutsionnoy morfologii analizatorov (The Historical Method and its
     Role in Deciding the Evolutionary Morphology of Analyzers). Thesis
     dissertation. VI. Vsesoyuzn. s'yezda anatomov, gistologov i
     embriologov (VIth All-Union Congress of Anatomists, Histologists, and
     Embryologists), Moscow, 1958, p. 18.

61. Vinokurov, V.A. Rol' grudnogo simpatikusa v peredache afferentnykh
     umpul'sov v legkikh. (Role of the Chest Sympathetic Nerve in the
     Transfer of Afferent Impulses to the Lungs). Collection of works of
     the Kuybyshev Medical Institute, Vol. 1, 1948, pp. 207-209.

62. Voytkevich, V.I. Oksigemometricheskaya issledovaniya arterial'noy krovi
     v zdorovom i bol'nom organizme (Oxyhemometric Studies of Arterial
     Blood in Healthy and Ailing Organisms). Author's abstract for disser-
     tation. Leningrad, 1952.

63. ―――――――――― The Influence of Muscular Load on Oxygen Saturation of
     Arterial Blood in Normal and Hypoxic Conditions. Fiziologicheskiy
     zhurnal SSSR, Vol. 41, No. 2, 1955, pp. 219-225.

64. ―――――――――― The Influence of Chronic Oxygen Starvation on the
     Dissociation Curve of Oxyhemoglobin of White Rats in a Number of Gener-
     ations. Fiziologicheskiy zhurnal SSSR, Vol. 49, No. 5, 1963,
     pp. 615-620.

65. ――――――――――. Certain Adaptive Reactions of the Human and Animal
     Blood Systems Under Conditions of Prolonged Oxygen Starvation. In:
     problemy kosmicheskoy meditsiny (Problems of Space Medicine), Moscow,
     1966, pp. 101-102.

66. Voskoboynikov, M.M., and P.P. Balabay. Comparative-Experimental Research
     on the Respiratory Apparatus of Bony Fish. Zbirnik prats z morfologii
     tvarin, Vol. 1-2, Kiev, 1934, pp. 5-49.

67. Gandel'sman, A.B. Motor Hypoxia. In: Kislorodnyy rezhim i yego
     regulirovaniye (The Oxygen Regime and its Regulation), Kiev-Kanev,
     1965, pp. 85-86.

68. Gandel'sman, A.B., and Yu.N. Verkhalo. Instrument Study of the Percep-
     tion of Shifts in the Internal Medium and the Efficiency of Motion
     Control in Severe Oxygen Deficiency. In: Problemy fiziologii sporta
     (Problems in the Physiology of Sports), Moscow, 1966, p. 5.

69. Gandel'sman, A.B., R.P. Gracheva, A.S. Yegorov, and A.T. Puni. Usloviya
     sovershenstvovaniya interotseptivnogo analiza, opredelyayushchiye
     osoznavayemost'ostrogo gipoksemicheskovo sdviga u chelovka (Conditions
     of Perfecting Interoceptor Analysis which Determines Perception of
     Severe Hypoxemic Shift in Man). XXI konf. po problemam vyssh. nervn.
     deyat. (XXIth Conference on Higher Nervous Activity). Moscow-
     Leningrad, 1966, pp. 85-86.

70. Gilyarov, M.S. Osobennosti pochvy kak sredy obitaniya i yeyoe znacheniye v evolyutsii nasekomykh (The Characteristics of Soil as an Inhabited Medium and its Significance in the Evolution of Insects), Moscow-Leningrad, 1949.

71. Golodov, I.I. K voprosu chuvstvitel'nosti dykhatel'nogo tsentra pri dykhanii gazovoy smes'yu, bogatoy kislorodom (Sensitivity of the Respiratory Center in Breathing Gas Mixtures Enriched with Oxygen). Tr. VMA im. S.M. Kirova (Transactions of the Military Medical Academy imeni S.M. Kirov), Vol. 35, 1941, pp. 57-64.

72. ————————. Methods of Studying Respiratory Conditioned Reflexes. Zhurnal vishney nervnoy deyatel'nosti, Vol. 9, No. 4, 1959, pp. 624-628.

73. Grechishkin, I.I. Napryazheniye kisloroda v tkani golovnogo mozga pri ingalyatsii 100% i 2% kisloroda (Oxygen Pressure in Brain Tissue upon Inhalation of 100% and 2% Oxygen). Tr. Orendurgsk. Otdèl. Vsesoyuzn fiziolog obshchestva (Works of the Orenburg All-Union Physiological Society). Vol. 3, 1964, pp. 67-73.

74. Gubler, Ye.V. Oxygen Consumption and Energy Expenditure in Artificial Hypothermy in Man. Vestnik khirurgii, Vol. 3, 1958, pp. 117-123.

75. ———————— The Role of "Natural" Hypothermy in Oxygen Starvation and the Influence of Low External Temperature. Uspekhi sovremennoy biologii, Vol. 53, No. 3, 1962, pp. 306-322.

76. Gurevich, M.I., and S.A. Berhteyn. The Role of Altered P_{O_2} in the Tissues in Regulating Local Blood Circulation in Severe Hypoxia. In: Problemy kosmicheskoy meditsiny (Problems in Space Medicine), Moscow, 1966, pp. 141-142.

77. Davydov, G.A. The Function of External Breathing in Mountain Acclimatization to Extreme Degrees of Rarified Atmosphere in an Altitude Chamber. In: Problemy kismicheskoy miditsiny (Problems in Space Medicine), Moscow, 1966, pp. 143-144.

78. Danko, Y.I. Kortikal'naya regulyatsiya dykhaniya u cheloveka i yeye ogranicheniya pri myshechnoy rabote (Cortical Regulation of Respiration in Man and its Limitation in Muscular Work). X s'yezd Vsesoyuzn. fiziolog. obshchestva (Xth Congress of the All-Union Physiological Society), Vol. 2, No. 1, Yerevan, 1964, p. 252.

79. ———————— Mechanisms of Adapting Respiration to Muscular Activity of Man. In: Dikhaniye i sport (Respiration and Sport), Tallin, 1967, p. 27.

80. Darenskaya, N.G., and G.M. Pravdin. Avoidance Responses of Animals to Radiation Fields. Byulleten eksperimental'noy biologii i meditsini, Vol. 65, No. 4, 1968, pp. 23-27.

81. Dedyulin, I.M. The Acid-Base Equilibrium Problem in the Human Organism with Decreased and Increased Partial Pressure of Oxygen. In: Gipoksiya (Hypoxia), Kiev, 1949, pp. 44-45.

82. Dembo, A.G. Nedostatochnost' funktsii vneshnego dykhaniya (Inadequacy of the External Breathing Function), Leningrad, 1957.

83. —————— . Classification of Respiratory Inadequacy and Basic Instrument Readings for differentiation of its Various Stages. Kazanskiy meditsinskiy zhurnal, Vol. 2, 1966, pp. 7-10.

84. Dembo, A.G., Z.A. Teslenko, and A.M. Tyurin. Some Data on Responses of External Breathing and Myocardium to Lowered Oxygenation of Arterial Blood in Healthy People. In: Kislorodnyy rezhim organizma i yego regulirovaniye (The Oxygen Regime and its Regulation), Kiev-Kanev, 1965, pp. 72-80.

85. Dianov, A.G., and A.G. Kuznetsov. The Possibility of Replacing Air Nitrogen with Helium in Spacecraft. In: Aviatsionnaya i kosmicheskaya meditsina (Aviation and Space Medicine), Moscow, 1963, pp. 162-165.

86. Dolina, O.A., M.N. Dubova, and S.V. Lokhvitsiy. The Use of Helium during Respiratory Insufficiency after Mixing in the Lungs. Eksperimental'naya khirurgicheskaya anesteziologiya, Vol. 11, No. 3, pp. 77-82.

87. Dolina, S.A. Influence of Differing Degrees of Hypoxia on Sensitivity to Epileptogenic Agents and Certain Functional Properties of Motor Formations of the Brain. Fiziologicheskiy Zhurnal SSSR, Vol. 51, No. 7, 1965, pp. 798-805.

88. Doronin, G.P. Some data on the study of valuable motor-conditioned reflexes during the prolonged existence of animals in an altered gas medium. In: Aviatsionnaya i kismicheskaya meditsina (Aviation and Space Medicine), Moscow, 1963, pp. 173-176.

89. Doroshchuk, V.I. Determining Respiratory Insufficiency. Terapevticheskiy Arkhiv, Vol. 37, No. 8, pp. 25-30.

90. Doyarenko, A.G. Studying Aeration of the Soil. Izvestiya Moskovskogo selskokhozyaystvennogo instituta, Vols. 1-2, 1915, pp. 1-45.

91. Zharov, S.G., Ye.A. Il'in, and Ye.A. Kovalenko. A Study of the Prolonged Effect on Man of an Atmosphere with Increased CO_2 Content. In: Aviatsionnaya i kosmicheskaya meditsina (Aviation and Space Medicine), Moscow, 1963, pp. 182-185.

92. Zheludkova, T.N., V.M. Zagruydskiy, and Z.K. Sulimo-Samuyllo. The Influence of Prolonged Existence in a Gas Medium with Increased Carbon Dioxide Content. In: Funktsii organizma v usloviyakh izmenemoy gasovoy sredy (Functions of an Organism in an Altered Medium), Vol. 3, Moscow-Leningrad, 1964, pp. 187-192.

93. Zhironkin, A.G. K analizu deystviya povyshennogo davleniya kisloroda na organisma (Analyzing the Effect of Increased Oxygen Pressure on an Organism), Author's abstract for dissertation. Leningrad, 1956.

94. Zhironkin, A.G., I.S. Breslav, E.A. Konza, A.M. Il'nitskiy, A.D. Nozdrachev, Ye.N. Salatsinskaya, G.V. Troshikhin, L.D. Fedorova, and A.M. Shmeleva. The Influence of Prolonged Existence of Animals in an Oxygen-Enriched Air Medium on Some Physiological Functions. Problemy kosmicheskoy biologii (Problems of Space Biology), Vol. 4, 1965, pp. 518-530.

95. Zhironkin, A.G., A.F. Panin, and N.A. Sorokin. Vliyaniye povyshennogo partial'nogo davleniya kisloroda na organizm cheloveka i zhivotnykh. (The Influence of Increased Partial Pressure of Oxygen on Man and Animals). Leningrad, 1965.

96. ——————————————————————————. Adaptive Response in Breathing Oxygen Under Pressure from 1 to 3 Atmospheres. In: Kislorodnyy rezhim organizma i yevo regulirovaniye (The Oxygen Regime and its Regulation), Kiev, 1966, pp. 311-316.

97. Zagryadskiy, V.P., and Z.K. Sulimo-Samuyllo. Protective Response Mechanisms and Their Impairment from the Effect of an Altered Gas Environment. In: Aviatsionnaya i kosmicheskaya medidsina (Aviation and Space Medicine), 1963, pp. 194-196.

98. Zal'tsman, G.L. Fiziologicheskiye osnovy prebyvaniya cheloveka v usloviyakh povyshennogo davleniya gazovoy sredy (Physiological Bases of Human Existence in a Gas Medium with Increased Pressure). Leningrad, 1961.

99. Zvorykin, V.N. Changes in Higher Nervous Activity in Rarified Air. Fiziologicheskiy Zhurnal SSSR, Vol. 39, No. 6, 1953, pp. 677-684.

100. Zilov, G.N. Vliyaniye povyshennogo partsial'nogo davleniya kisloroda na vyshuyu nervnuyu deyatelnost (The Influence of Increased Partial Pressure of Oxygen on Higher Nervous Activity). Tez. Dokl. 16-go soveshch. po problemam vyssh. nervn. deyat. (Dissertation thesis for the 16th Conference on Higher Nervous Activity), Moscow-Leningrad, 1953, pp. 90-91.

101. Ivanov, K.P. Oxygen Consumption and Change in the Skeletal Muscles during Hypoxia. Fiziologicheskiy zhurnal SSSR, Vol. 45, No. 8, 1959, pp. 988-993.

102. ——————— Physiological Mechanisms of Altered Oxygen Consumption and Body Temperature during Hypoxia. In: Kislorodnyy rezhim organizma i yevo regulirovaniye (The Oxygen Regime and its Regulation), Kiev, 1966, pp. 219-224.

103. ——————— Kislorodnoye golodaniye i temperatura tela. (Oxygen Starvation and Body Temperature), Leningrad, 1968.

104. Ivanov, Yu.N. Sravnitel'naya chuvstvitel'nost' kory golovnogo mozga i prodolgovatogo mozga k deystviyu CO_2 po dannym bioelektricheskikh reaktsiy (Comparative Sensitivity of the Cortex and the Medulla Oblongata to the Effect of CO_2, According to Data from Bioelectric Responses), 2-ya Povolzhsk. konf. fiziologov, biokhimikov i farmakologov (2nd Volga Conference of Physiologists, Biochemists, and Pharmacologists), Kazan, 1961, pp. 217-218.

105. ———————— Vliyaniye fiziologicheskikh sostoyaniy kory golovnogo mozga na chuvstvitel'nost' organizma k CO_2 (The Influence of the Physiological Condition of the Cortex on Sensitivity of the Organism to CO_2). Tez. 48-y itogovoy nauchn. konfer. (Thesis for the 48th Summary Scientific Conference). Astrakhan Medical Institute, 1966, pp. 178-179.

106. Ivanov, Yu.N., and P.Ye. El'gort. Reaktsiya dykhaniya, krovoobrashcheniya i krovi pri izmeneniyakh funktsional'nogo sostoyaniya kory golovnogo mozga (Response of Respiration, Blood Circulation, and Blood to Changes of the Functional Condition of the Cortex of the Brain). Tez. 48-y itogovoy nauchn. konfer. (Thesis for the 48th Summary Scientific Conference). Astrakhan Medical Institute, 1966, pp. 176-177.

107. Il'in, Ye.A. Dynamics of P_{O_2} in Various Brain Structures During Oxygen Respiration under Normal Conditions, after Transmitted Anoxia and in Disturbed Blood Circulation of the Brain). In: Problemy kosmicheskoy meditsiny (Problems of Space Medicine), Moscow, 1966, pp. 181-182.

108. Ioseliani, K.K. Rapid Mental Activity of Man during Hypoxia. Voyenno-meditsinskiy zhurnal, Vol. 10, 1967, pp. 83-86.

109. Isayev, G.G.   Nekotoryye dannyye k analizu dvigatel'noy arterial'noy gipoksemii (Some Data for Analyzing Motor Arterial Hypoxemia). Materialv X Vsesoyuzn. konf. po fiziologii, morfologii, biomekhanike i biomekhimii myshechnoy deyatel'nosti (Data from the Xth All-Union Conference on the Physiology, Morphology, Biomechanics, and Biochemistry of Muscular Activity), Vol. 2, Moscow, 1968, pp. 18-19.

110. Kalabukhov, N.I. The Relationship of the Thermotactic Optimum and "Critical" Temperature in Mammals. Uspekhy sovremennoy biologii, Vol. 10, No. 3, 1939, pp. 540-542.   /148

111. Kartashevskiy, Y.A. O vliyanii nedostatka kisloroda na obmen veshchestv i teploproizvodstvo v zhivotnom organizme. (The Effect of an Insufficience of Oxygen on Metabolism and Heat Production in the Living Organism Dissertation, St. Petersburg, 1906.

112. Kassil', V.G. Vzaimosvyaz' mezdu rabotoy pishchevogo i pit'yevogo
     tsentrov i sostoyaniyem pishchevaritel'nogo kanala (The Relation
     Between the Work of the Food and Drink Centers and The Condition of
     the Alimentary Canal). X s'yezd. Vsesoyuzn. Fiziolog. ob-va (X[th]
     Conference of the All-Union Physiology Society), Vol. 2, No. 1,
     Yerevan, 1964, p. 371.

113. ——————— Zheludochno-kishechnyy trakt i pishchevoye novedeniye
     (The Digestive-Intestinal Tract and Food Behavior), Dissertation,
     Leningrad, 1969.

114. Kassil'. V.G., A.M. Ugolev, and V.N. Chernigovskiy. Potrebleniye pishchi
     i obmen vesnchestv (Food Consumption and Metabolism). X s'yezd.
     Vsesoyuzn. fiziolog. obshch. (X[th] Conference of the All-Union ·
     Physiology Society), Vol. 1, Yerevan, 1964, p. 118.

115. Klossovskiy, B.N. Tsirkulyatsiya krovi v mozgu (Blood Circulation in the
     Brain), Moscow, 1951.

116. Kovalenko, Ye.A. The Influence of a Highly Rarified Atmosphere on
     Oxygen Pressure in Brain Tissues). Fiziologicheskiy zhurnal SSSR,
     Vol. 48, No. 2, 1963, pp. 150-157.

117. Kovalenko, Ye.A., F.V. Babchinskiy, and I.N. Chernyakov. Oxygen Saturation
     of the Blood and Oxygen Pressure in Brain Tissues During Respiration of
     a Rarified Atmosphere, In: Novoye v fiziologii i patologii dykhaniya
     (New Developments in the Physiology and Pathology of Respiration),
     Kiev, 1961, pp. 97-99.

118. Kovalenko, Ye.A., V.L. Popkov, and I.N. Chernyakov. Oxygenation of Brain
     Tissues during Respiration of Air and Oxygen with an Admixture of CO_2.
     Fiziologicheskiy znurnal SSSR, Vol. 50, No. 2, 1964, pp. 177-182.

119. Kolchinskaya, A.Z. The Age Factor in Adaptation of the Human Organism
     to Insufficient Oxygen. In: Kislorodnaya nedostatochnost' (Oxygen
     Insufficiency), Kiev, 1963, pp. 42-51.

120. ——————— Classification of Degrees of Hypoxic Conditions.
     In: Kislorodnaya nedostatochnost' (Oxygen Insufficiency), Kiev, 1963,
     pp. 558-562.

121. ———————. Nedostatok kisloroda i vozrast (Insufficient Oxygen
     and Age), Kiev, 1964.

122. Kolyakina, E.A.   Gazoobmen i oykhaniye pri izmeneniyakh dykhatel'nykh
     dvizheniy po slovesnoy instruktsii (Gaseous Exchange and Respiration
     during Altered Respiratory Movements by Verbal Instructions). Author's
     abstract for dissertation. Leningrad, 1967.

123. Konza, E.A. K voprosu o termoregulyatsii zhivotnykh v helio-kislorodnoy atmosfere (Thermal Regulation of Animals in a Helium-Oxygen Atmosphere). DAN SSSR, Vol. 165, No. 4, 1965, pp. 959-961.

124. Konradi, G.P., and Z.V. Bebeshina. The Formation of Conditioned Reflexes in Activating the Respiratory Center. Arkhiv biologicheskikh nauk, Vol. 38, No. 2, pp. 243-251.

125. Konradi, G.P., A.D. Slonim, and V.S. Farfel'. Obshchiye osnovy fiziologii truda (General Principles of the Physiology of Work), Moscow-Leningrad, 1934.

126. Konstantinov, V.A., M.A. Alimbayeva, and V.I. Tsitsurin. The Impairment of Thermal Regulation in Rabbits during Hypoxia Induced at Various Rates. Patologicheskaya fiziologiya i eksperimental'naya terapiya, Vol. 12, No. 3, 1968, pp. 55-60.

127. Korol'kov, V.I., Ye.A. Kovalenk, and Ye.A. Il'ina. Ob osobennostyakh oksigenatsii miokarda pri deystvii nekotorykh ekstremal'nykh faktorov (Characteristics of Oxygenation of the Myocardium under the Effect of Several Extreme Factors). X s'yezd Vsesoyuzn. fiziolog. obshch. (Xth Conference of the All-Union Physiology Society), Vol. 2, No. 1, Yerevan, 1964, p. 410.

128. Kocherga, D.A. New Data on the Functional Organization of the Respiratory Center and Mechanisms of Respiratory Movement Coordination. In: Kislorodnyy rezhim organizma i yevo regulirvaniye (The Oxygen Regime and its Regulation), Kiev-Kanev, 1965, pp. 135-137.

129. Kocherga, D.A. Mechanism of the Influence of the Cortex on Respiratory Movements. Fiziologicheskiy zhurnal, Academy of Sciences, Ukrainian SSR, Vol. 12, No. 5, 1966, pp. 661-668.

130. Kravchinskiy, B.D. Automatism and Reflex in Respiratory Center Activity in Vertebrate Animals. Uspekhy sovremennoy biologii, Vol 19, No. 3, pp. 291-315.   /14

131. Krasnov, Ye.A. Conditioned Reflex Regulation of Respiration in Ontogenesis. Nauchnaya izvestiya, Kazakh Medical Institute, Vol. 11, 1953. pp. 8-13.

132. Kreps, Ye.M. Oksigemometriya (Oxyhemometrics). Leningrad, 1959.

133. Krylov, S.S. Two Chemoreceptor Mechanisms of the Carotid Bodies. In: Kislorodnaya nedostatochonost' (Oxygen Insufficiency), Kiev, 1963, pp. 228-234.

134. ————— The Role of Chemoreceptors in Carotid Bodies in Regulating Pulmonary Respiration. In: Kislorodnyy rezhim organizma i yevo regulirovaniye (The Oxygen Regime and its Regulation), Kiev, 1966, pp. 99-192.

135. Kudryavtsev, Ye.V. O kortikal'nykh svyazyakh meshdu dykhaniyem i myshechnoy deyatel'nost'yu (Cortical Relationships between Respiration and Muscular Activity). Author's abstract for dissertation. Moscow, 1953.

136. Kuznetsova, Z.P.   Vyrabotka uslovnykh refleksov s khimioretseptorov na vdykhaniye kisloroda (The Development of Conditioned Reflexes from Chemoreceptors during Oxygen Respiration). Sb. tr. Omsk. filiala Vsesoyuzn. obshch. fiziologov, biokhimikov i farmakologov. (Collection of Works of the Omsk Branch of the All-Union Society of Physiologists, Biochemists and Pharmacologists), Vol. 1, 1958, pp. 119-123.

137. Kulik, A.M. Regulyatsiya dykhaniya pri raznykh vozdeystviyakh na organism (Respiration Regulation during Various Activities of an Organism). Author's abstract for dissertation, Moscow, 1967.

138. Kumanichkin, S.D. Human Physical Efficiency under Pressure in Conditions of Breathing Air-Oxygen and Air-Helium Mixtures. Voyenno-meditsinksiy zhurnal, Vol. 11, 1960, pp. 77-80.

139. Kucheruk, V.V. Burrows as Protection from Unpleasant Effects of Abiotic Factors in an Environment. In: Fauna i ekologiya gryzunov (Fauna and Ecology of Rodents). Moscow, 1960, pp. 56-95.

140. Lavrent'yev, B.I. Sensitive Innervation of the Internal Organs. Zhurnal obshchey biologii, Vol. 4, No. 4, 1943, pp. 232-252.

141. Lazarev, N.V. Khimicheski vrednyye veshchestva v promyshlennosti, 2. Kislorod (Chemically Harmful Substances in Industry, 2. Oxygen). Leningrad, 1960.

142. Lang, G.F.   Bolyezni sistemy krovoobrashcheniya (Diseases of the Circulatory System). Moscow, 1958.

143. Lauer, N.V. The Age Factor in Response to Hypoxia. In: Kislorodnaya nedostatochnost' (Oxygen Insufficiency), Kiev, 1963, pp. 34-40.

144. Lauer, N.V., and A.Z. Kolchinskaya. The Oxygen Regime. In: Kislorodnyy rezhim organizma i yego regulirovaniye (The Oxygen Regime and its Regulation), Kiev, 1966, pp. 3-15.

145. Lashkov, V.F. Innervatsiya organov dykhaniya (Innervation of Respiratory Organs), Moscow, 1963.

146. Lebedeva, V.A. Nekotoryye aspekty problemy khemoretseptsii. (Some Aspects of the Problem of Chemoreception). X s'yezd Vsesoyuzn. Fiziolog. obshch. (X[th] Congress of the All-Union Physiology Society), Vol. 1, Yerevan, 1964, pp. 106-107.

147. ——————— Mekhanizmy khemoretseptsii (Chemoreception Mechanisms), Leningrad, 1965.

148. Letunov, S. P. Hypoxic Conditioning as a Means of Increasing Efficiency. In: Akklimatizatsiya i trenirovka sportsmennov v gornoy mestnosti (Acclimatization and Training of Athletes in Mountain Areas), Alma-Ata, 1965, pp. 59-61.

149. Liberman, V.B., and G.A. Trubitsina. The Interaction of Signalling Systems in Muscular Work. In: Opyt izucheniya regulyatsiy fiziologicheskikh funktsiy (Research Experience in Regulating Physiological Functions), Vol. 3, Moscow-Leningrad, 1954, pp. 259-266.

150. Lifshitz, A.V. The Influence of Hypoxemia on Higher Nervous Activity. Fiziologicheskiy zhurnal SSSR, Vol. 35, No. 1, 1949, pp. 3-15.

151. Lopatina, N.M. Znacheniye retseptornykh poley srednego otdela dykhatel' nogo trakta dlya regulyatsii dykhaniya (The Significance of Receptor Fields in the Central Respiratory Tract in Regulating Respiration). Tr. Kuybyshevsk. med. inst. (Works of the Kuybuyshev Medical Institute), Vol. 1, 1948, pp. 210-212.

152. Lyundegord, G. Vliyaniye klimata i pochvy na rost rasteniy (The Influence of Climate and Soil on Plant Growth), Moscow, 1937.

153. Magazinnik, N.A. Shortness of Breath and the Work Expended in Ventilation of the Lungs. Klinicheskaya meditsina, Vol. 40, No. 12, 1962, pp. 93-100.

154. Malkin, V.B. From the Cave of Prehistoric Man to the Spacecraft. The Atmosphere of Closed Spaces. Nauka i zhizn', Vol. 8, 1968, pp. 81-89.

155. Malova, M.N. The Influence of Oxygen Therapy on External Respiration and Oxygen Saturation of Arterial Blood in Chronic Heart-Lung Diseases. Sovremennaya meditsina, Vol. 1, 1962, pp. 39-43.

156. Marshak, M.Ye. Current Stage of Regulating Human Respiration. uspekhy sovremennoy biologii, Vol. 30, No. 2, 1950, pp. 161-175.

157. ——————. Regulyatsiya dykhaniya u cheloveka (Regulation of Human Respiration), Moscow, 1961.

158. ——————. Local Oxygen Insufficiency. In: Kislorodnaya nedosta-tochnost' (Oxygen Insufficiency), Kiev, 1963, pp. 224-227. /150

159. Marshak, M.Ye., L.I. Ardashnikova, G.N. Aronova, A.M. Blinova, and M.M. Voll. The Influence of Carbon Dioxide during Hypoxemia on Blood Circulation and Oxygen Consumption in Various Organs. In: K regulyatsii dykhaniya, krovoobrashcheniya i gazoobmena (Regulation of Respiration, Blood Circulation and Gaseous Exchange), Moscow, 1948, pp. 65-90.

160. Myasnikov, A.I. Osnovy diagnostiki i chastnoy patologii (propedevtika) vnutrennikh bolezney (Basic Diagnostics and Special Pathology [Propaedeutics] of Internal Diseases). Moscow, 1952.

161. Okuneva, G.N. O vliyanii izmeneniy davleniya v izolirovannykh karotid-
nykh sinusakh i zheludochkakh mozga (no metodu Golovina) na dykhaniye
i krovyanoye davleniye (The Influence of Pressure Changes in Isolated
Carotid Sinuses and Brain Ventricles [According to the Golovina Method]
on Respiration and Blood Pressure). Konf. molodykh nauchn. rabotnikov
Kuybyshevsk. med. inst. (Conference of Young Scientists of the
Kuybuyshev Medical Institute), 1960, pp. 51-52.

162. Orbeli, L.A., B.V. Kravshinskiy, K.A. Pavlovskiy, and S.P. Shistovskiy.
Deystviye azota i geliya na cheloveka pri pobyshennom atmosfernom
davlenii (The Effect of Nitrogen and Helium on Man under Increased
Atmospheric Pressure). Tez. mezhkafedral'n. nauchn. konf. VMA im.
S.M. Kirova (Abstracts of the Interdepartmental Scientific Conference of
the S.M. Kirov Medical Military Academy), Leningrad, 1940, pp. 31-32.

163. Orlov, V.N. Medisinksiy kislorod (Medical Oxygen). Moscow, 1959.

164. Osipova, O.V. Physiological Principles of the Effect of Respiratory
Exercises. In: Voprosy fizicheskoy kultury (Questions of Physical
Culture). Leningrad, 1960, pp. 14-24.

165. Pavlov, I.P. Dvatsatiletniy opyt izucheniya vyshey nervnoy deyatel'nosti
zhivotnykh (Twenty Years of Research on the Higher Nervous Activity of
Animals). Moscow-Petrograd, 1923.

166. Pavlovskiy, Ye.N. K voprosu o roli verkhnikh dykhatel'nykh putey v
regulyatsii dykhaniya. (The Role of the Upper Respiratory Tract in
Respiration Regulation). Tr. Tatarsk. inst. teoretich. i klinich. med.
Kazan' (Works of the Tatar Institute of Theoretical and Clinical Medi-
cine), Kazan', Vol. 4, No. 4, 1937, pp. 135-167.

167. Petrov, I.R. Kislorodnoye golodaniye golovnogo mozga. (Oxygen Starvation
of the Brain). Leningrad, 1949.

168. Povedeniye i retseptsii ryb (Behavior and Reception of Fish), Moscow, 1967.

169. Pogrebkova, A.V. Dykhatelnyye uslovnyye refleksy pri vyklyuchenii
distantnykh retseptorov (Respiratory Conditioned Reflexes with Non-
Operating Range Receptors). 18-e soveshch. po probl. vyssh. nervn.
deyat. (18th Conference on Higher Nervous Activity), Vol. 3, Leningrad,
1958, p. 71.

170. ─────────────. The Role of Sigma-Shaped Convolutions of the Cortex of
the Brain in Regulating Respiration. Zhurnal vysshikh nervnikh
deyatel'nostyei, Vol. 15, No. 5, 1965, pp. 919-926.

171. Pozdnyakova, R.A. The Influence of Oxygen Starvation on Interoceptive
Reflexes. In: Kislorodnaya Nedostatochnost' (Oxygen Insufficiency),
Kiev, 1963, pp. 235-240.

172. Privol'nev, T.I. Respiration Change in Ontogenesis of Fish for Various
     Levels of Oxygen Partial Pressure. Izvestiya VNIIORKh (All-Union
     Scientific Research Institute of Organic Chemistry), Vol. 25, No. 1,
     1947, pp. 58-112.

173. Privol'nev, T.I. Respiration of Fish as a Factor Causing Their Distribu-
     tion in a Reservoir. Isvestiya VNIIORKh, Vol. 25, No. 2, 1948,
     pp. 125-148.

174. Puchkov, N.V.   Fiziologiya ryb (Physiology of Fish). Moscow, 1954.

175. Repin, I.S.   Ismeneniye mozgovykh potentsialov v khode prisposoble-
     niya k giperkapnii. (Change of Brain Potential in the Course of
     Adapting to Hypercapnia). Materialy konfer. p probl. adaptatsii i dr.
     sposobam povysheniya ustoychivosti organizma (Material from the Confer-
     ence on Adaptation and Other Means of Increasing an Organisms' Resistance)
     Vinnitsa, 1962, p. 86.

176. ——————————— Analyzing the Mechanism of the Effect of Hypoxia and
     Hypercapnia on the Central Nervous System. In: Kislorodnyy rezhim
     organizma i yego regulirovaniye (The Oxygen Regime and its Regulation),
     Kiev-Kanev, 1965, pp. 229-230.

177. Rickl', A.V., and N.K. Krivosheyenko. Vliyaniye povyshennogo atmosfernogo
     davleniya na vyshnuyu nernuyu deyatel'nost' (The Influence of Increased
     Atmospheric Pressure on Higher Nervous Activity). Tr. nauchn. sessii
     VMMA, posvyashch. 30-letiyu Velikoy Oktyabr'skoy revol. (Works of the
     Naval Medical Academy Scientific Conference Dedicated to the 30th
     Anniversary of the October Revolution), Leningrad, 1948, pp. 62-69.

178. Rossolovskiy, N.A. Nekotoryye voprosy fiziologii voyennogo truda i
     akklimatizatsii v usloviyakh gornogo klimata Pamira i Tyan'Shanya
     (Some Questions on the Physiology of Military Work and Acclimatization
     to the Mountain Climate of Pamir and Tien Shan). Author's abstract
     of dissertation. Leningrad, 1958.

179. Savich, A.A. Dal'neyshiye materialy p voprosu o vliyanii pishchevykh
     refleksov drug na druga (Futher Data on the Influence of Food Reflexes
     on Each Other). Dissertation. St. Petersburg, 1913.

180. Sagalovich, B.M. Fiziologiya i patofiziologiya verkhnikh dykhatel'nykh
     putey (Physiology and Pathophysiology of the Upper Respiratory Tract),
     Moscow, 1967.

181. Salatsinskaya, Ye.N. The Influence of Athletic Training and Acclimatiza-
     tion to High-Mountain Conditions on Human Resistance to Hypoxia.
     Ucheniye zapiski Kabardino-Balka University (Scientific Reports of the
     Karbadino-Balkarskiy University), Vol. 33, 1967, pp. 209-210.

174

182. Sanotskaya, N.V. The Influence of Carbon Dioxide on Oxygen Pressure in the Brain and Skeletal Muscles During Severe Hypoxia. Byulleten eksperimental'noy biologii i meditsini, Vol. 54, No. 9, pp. 46-49.

183. ———————— Vliyaniye gipoksii i giperkapnii na napryazheniye kisloroda v tkanyakh mozga, miokarda i skeletnoy myshtse (The Influence of Hypoxia and Hypercapnia on Oxygen Pressure in Brain Tissues, Myocardium and Skeletal Muscles). Materialy konf. po probl. adaptatsii, trenirovki i dr. sposobam povysheniya ustoychivosti organizma (Data from the Conference on Adaptation, Conditioning, and Other Means of Increasing an Organism's Resistance), Vinnitsa, 1962, p. 89.

184. ———————— The Influence of Carbon Dioxide on Oxygen Pressure in the Myocardium. Fiziologicheskiy zhurnal SSSR, Vol. 52, No. 5, pp. 556-561.

185. Sepp, Ye.K. Istoriya razvitiya nervnoy sistemy pozvonochnykh (History of the Development of the Nervous System in Vertebrates)., Moscow, 1949.

186. Serbenyuk, Ts.V. Mekhanizm vneshnego dykhaniya nizshikh pozvonochnykh (Mechanism of External Respiration in Lower Vertebrates). Author's abstract for dissertation. Moscow, 1968.

187. Sergeyev, A.A. Mekhanicheskoye i khmicheskoye vliyaniy razrezhennogo vozdukha po chelovecheskiy organizm (Mechanical and Chemical Influence of Rarified Air on the Human Organism). Moscow, 1926.

188. ———————— The Influence of Severe Oxygen Insufficiency on the Cardio-Vascular System. Gigienichnaya truda i tekhnicheskaya bezopastnost', Vol. 1, 1935, pp. 5-12.

189. ———————— Ocherki po istorii aviatsionnoy meditsiny (Essays on the History of Aviation Medicine). Moscow-Leningrad, 1962.

190. Sergiyevskiy, M.V. New Data on Respiration Regulation. In: Novoye v fiziologii i patologii dykhaniya (New Developments in the Physiology and Pathology of Respiration), Moscow, 1961, pp. 188-200.

191. ———————— O nekotorykh spornykh voprosakh regulyatsii dykhaniya (Several Controversial Questions on Respiration Regulation), Materialy 6-y nauchn. konf. po vopr. vozrastnoy morfologii, fiziologii i biokhimii (Data from the 6th Scientific Conference on Age Morphology, Physiology and Biochemistry). Moscow, 1963, pp. 462-463.

192. ———————— Respiration Regulation Normally and During Hypoxia, Ucheniye zapiski, Kabardino-Balkar.Universiteta, Vol. 33, 1967, pp. 25-36.

193. Sergiyevskiy, M.V., and Yu.N. Ivanov. Kratiy obzor issledovaniy po
fiziologii dykhaniya za posledniye 10 let. (A Short Survey of Research
in the Physiology of Respiration in the Last 10 Years). Kuybuyshev,
1961.

194. Seredenko, M.M. Some Special Responses of a Senile Organism to Severe
Hypoxia. In: Kislorodnaya nedostatochnost' (Oxygen Insufficiency),
Kiev, 1963, pp. 79-85.

195 Sechenov, I.M. Refleksy golovnogo mozga (Reflexes of the Brain).
St. Petersburg, 1866.

196 ——————— Teoriya Sostava logochnoga vozdukha (Theory of the
Composition of Lung Air), Selected works, Moscow, 1935, pp. 52-59.

197. Sirotinin, N.I. The Significance of Hypoxia in Early Signs of Aging.
Zhurnal patologicheskoy fiziologii i eksperimentalnoy terapii,
Vol. 10, No. 3, 1966, pp. 8-11.

198. Slonim, A.D. Zhivotnaya teplota i yeye regulyatsiya v organizme
mlekopitayushchikh. (Animal Heat and its Regulation in Mammals).
Moscow-Leningrad, 1952.

199. ——————— Osnovy chastnoy ekologischeskoy fiziologii mleko-
pitayushchykh (Principles of Special Ecological Physiology of Mammals),
Part 2, Leningrad, 1962.

200. ——————— Instinkt. Zagadki vrozhdennogo povendinya organizmov
(Instinct. The Strange Natural Behavior of Organisms). Leningrad,
1967.

201. Smirenskaya, Ye.M. Carbogen in the Treatment of Terminal Cases.
Vestnik khirurgii, Vol. 74, No. 1, 1954, pp. 5-10.

202. Smirnov, K.M., B.D. Asafov, and O.V. Osipova. The Electrical Activity
of the Speech Muscles during Respiratory and Motor Responses.
Fiziologicheskiy zhurnal SSSR, Vol. 48, Vol. 11, pp. 1325-1331.

203. Smirnov, K.M., E.A. Kolyakina, S.D. Kuznetsova, and V.A. Svetlichnaya.
O kortikal'nykh vliyaniyakh v regulyatsii dykhaniya u cheloveka
(Cortical Influences in Human Respiration Regulation) 21-e soveshch.
po probl. vyssh. nervn. deyat. (21st Conference on Higher Nervous
Activity), Moscow-Leningrad, 1966, p. 275.

204. Smirnov, K.M., O.V. Osipova, and A.I. Osipov. O proizvol'noy regulyatsii
dykhaniya u cheloveka i o yeye izmeneniyakh v protsesse uprazhneniya
(Arbitrary Respiration Regulation in Man and its Changes during
Exercise). X s'vezd Vsosoyuzn. Fiziolog. obshch. (Xth Congress of
the All-Union Physiology Society), Vol. 2, No. 2, Yerevan, 1964,
pp. 277-278.

205. Sokolov, V.A. Gazy Zemli (Gases of the Earth). Moscow, 1966.

206. Sorinson, S.N. Characteristics of Respiration Changes during Oxygen Inhalation by Chronic Respiratory Disease Patients and their Clinical Significance. Terapiya Archiv, Vol. 32, No. 4, 1960, pp. 77-84.   /152

207. ——————. Oxygen Therapy in Chronic Respiratory Diseases. Kazanskiy meditsinskiy zhurnal, Vol. 2, 1966, pp. 25-27.

208. Sorokin, P.A. Vliyaniye vysokikh davleniy kisloroda i vodolaznykh spuskov na sistemu krovoobrashcheniya (The Influence of High Oxygen Pressure and Divers' Descents on the Circulatory System). Author's abstract for dissertation. Leningrad, 1960.

209. Starkov, V.V. The Mechanism of Respiration Change during Hypothermy. In: Novoye v fiziologii i patologii dykhaniya (New Developments in Physiology and Pathology of Respiration), Moscow, 1961, pp. 205-206.

210. Stroganov, V.V. Deystviye uslovnykh i natural'nykh razdrazhiteley pri nasyshchenii (The Effect of Conditioned and Natural Stimuli with Saturation). Tr. fiziol. labor. A.P. Pavlova (Works of the Physiology Laboratory of the I.P. Pavlov Academy), Vol. 3, Nos. 2-3, 1929, pp. 117-132.

211. Troshikhin, G.V. The Effect of an Hyperoxic Medium on Some Physiological Functions of a Living Organism. Fiziologicheskiy zhurnal, Akademiya Nauk, USSR, Vol. 12, No. 3, 1966, pp. 313-320.

212. ——————— The Influence of Helium on Conditioned Reflex Activity and Gaseous Exchange in Animals. In: Problemy kosmicheskoy meditsiny (Problems in Space Medicine), Moscow, 1966, pp. 366-367.

213. Trumpayts, Ya.I., and S.L. Kaminskiy. Fiziologicheskoye obosnovaniye dopustimogo sporotivleniya dykhaniy pri rabote v respiratore (Physiological Basis of Permissible Resistance during Respiratory Work). Materialy V Vsesoyuzn. konf. po fiziologii truda (Data from the Vth All-Union Conference on Physiological Work). Moscow, 1967, pp. 296-297.

214. Tushinskiy, M.D., A.Ya. Tsigel'nik, and K.A. Shchukarev. Bolezni sistemy dykhaniya (Diseases of the Respiratory System). Leningrad, 1960.

215. Uspenskiy, P.I. The Signficance of Oxygen in the Treatment of Nervous Diseases. Zhurnal normalnoy i patologicheskoy gistologii i farmakologii, Vol. 2, 1870, pp. 137-150.

216. Fel'berbaum, R.A. Reflector Influences from the Upper Respiratory Tract. Fiziologicheskiy zhurnal SSSR, Vol. 49, No. 6, 1963, pp. 736-743.

217. Frankshteyn, Z.I., and Z.N. Sergeyeva. Samoregulyatsiya dykhaniya v norme i patologii (Normal and Pathological Self-Regulation of Respiration). Moscow, 1966.

218. Fudin, N.A. Proizvol'naya regulyatsiya dykhaniya kak metod vosstanov-
      leniya yego narusheniy u bol'nykh tuberkulezom (Arbitrary Regulation
      of Respiration as a Method of Restoring Breathing Damage in Tubercular
      Lungs). Author's abstract for dissertation. Leningrad, 1967.

219. Halifman, I. Two Hours from Ashkhabad. In: Puti v neznayemoye
      (Journeys to the Unknown), Vol. 2, Moscow, 1962, pp. 98-130.

220. Haldane, J.S., and J.G. Priestley. Respiration. Translated from
      English. Leningrad, 1937.

221. Chernigovskiy, V.N. Receptors of the Cardio-Vascular System. Uspekhi
      sovremennoy biologii, Vol. 23, No. 2, 1947, pp. 215-240.

222. ——————————— Interotseptory (Interoceptors). Moscow, 1960.

223. Chernov, V.M. Karbogen i yego primeneniye v meditsinskoy praktike
      (Carbogen and its Use in Medical Practice). Moscow, 1943.

224. Chernorutskiy, M.V. Diagnostika vnutrennikn bolezney (Diagnostics of
      Internal Diseases), Leningrad, 1954.

225. Chernyakov, I.N. The Velocity of the Blood Flow in Man at High
      Altitudes while Breathing Rarified Air and Oxygen at Increased
      Pressure. Voyenno-meditsinksiy zhurnal, Vol. 11, 1960, pp. 68-70.

226. Shik, L.L. The Significance of Hypocapnia and its Prevention in Lowered
      Partial Pressure of Oxygen. In: Gipoksiya (Hypoxia) Kiev, 1949,
      pp. 46-56.

227. ——————— Oxygen Starvation and its Compensation Mechanisms in Congeni-
      tal Defects of the Blue and Pale Type. In: Kislorodnaya nedostatoch-
      nost' (Oxygen Insufficiency), Kiev, 1963, pp. 253-258.

228. ——————— Oxygen Demand and Blood Circulation. In: Kislorodnyy
      rezhim organizma i yego regulirovaniye (The Oxygen Regime and its
      Regulation), Kiev, 1966, pp. 103-108.

229. Aber, G.M., A.M. Harris, and J.M. Bishop. The Effect of Acute Changes
      in Inspired Oxygen Concentrations on Cardiac, Respiratory and Renal
      Functions in Patients with Chronic Obstructive Airways Diseases.
      Clin. Sci., Vol. 26, 1964, pp. 133-143.

230. Ackerman, V.B., and F.B. Brincley. Oxygen Tensions in Normal and
      Ishemic Tissues during Hyperbaric Therapy. J. Amer. Med. Assoc.,
      Vol. 198, 1966, pp. 1280-1283.

231. Albano, G., and C. Ciulla. Prime osservazioni sperimentali di una
      sindrome cardiovasculatoria da respirazione iperbarica de elie (First
      Experimental Observations of a Cardiovascular Syndrome of Helium
      Respiration). Boll. Soc. Ital. Biol. Sperim., Vol. 42, 1966,
      pp. 1248-1250.

232. Albano, G., and T. Indovina. Effetti dell'iperpressione ambientale sull'organismo umano. (Effect of Ambient Hyperpressure on the Human Organism). Folia Med., Vol. 9, 1962, pp. 785-804.

233. Altland, P.D., H.F. Brubach, and M.G. Parker. Effects of Inert Gases on Tolerance of Rats to Hypoxia. J. Apply. Physiol., Vol. 24, 1968, pp. 778-781.

234. ———————————————————————, and B. Highman. Blood Gases and Acid-base Values of Unanesthetized Rats Exposed to Hypoxia Amer. J. Physiol., Vol. 212, 1967, pp. 142-148.

235. Anderton, L.L., and E.A. Harris. The Changing State of Breathing During Inhalation of CO_2, Studied with an Inexpensive Recording CO_2-analyzer. Quart. J. Exptl. Physiol., Vol. 48, 1963, pp. 1-12.

236. Anthony, A.Y. Über Sauerstoffatmung (Oxygen Respiration). Deutsche Med. Wschr., Vol. 66, 1940, pp. 482-484.

237. Archibald, E.R. The Carbon Dioxide Response Curve of the Dog at Sea Level and at Altitude. Biol. Abstr., Vol. 46, No. 96770, 1964.

238. Armstrong, B.W., H.H. Hurt, R.W. Blide, and J.M. Workman. The Humoral Regulation of Breathing. Science, Vol. 133, 1961, pp. 1897-1906.

239. Armstrong, H.G. Principles and Practice of Aviation Medicine. London, 1952.

240. Asmussen, E. On the Nervous Factors Controlling Respiration and Circulation During Exercise. Acta Physiol. Scand., Vol. 63, 1965, pp. 343-350.

241. Asmussen, E., E.H. Christensen, and M. Nielsen. Humoral or Nervous Control of Respiration During Muscular Work? Acta Physiol. Scand., Vol. 6, 1943, pp. 160-167.

242. Asmussen, E., and M. Nielsen. Pulmonary Ventilation and Effect of Oxygen Breathing in Heavy Exercise. Acta Physiol. Scand., Vol. 43, 1958, pp. 365-378.

243. Avery, M.E., V. Chernick, and M. Young. Fetal Respiratory Movements in Response to Rapid Changes of CO_2 in the Carotid Artery. J. Appl. Physiol., Vol. 20, pp. 225-227.

244. Babak, E. Zur Frage über das Zustandekommen der Atembewegungen der Fischen (The Mechanics of Fish Breathing Motions). Zbl. Physiol., Vol. 21, 1907, p. 17.

245. Bailen, H.M., and S.M. Hovvath. Evaluation of Neurogenic and Metabolic Influence From a Perfused Leg on Respiratory Exchanges. Amer. J. Physiol., Vol. 196, 1959, pp. 467-469.

246. Banus, M., H. Corman, V. Perlo, and G. Popkin. The Sensitivity of the Respiratory Center to Hydrogen Ion Concentration. Amer. J. Physiol., Vol. 142, 1944, pp. 121-130.

247. Barach, A. Use of Helium as a New Therapeutic Gas. Proc. Soc. Exptl. Biol. Med., Vol. 32, 1934, p. 462.

248. ———— The Effect of Inhalation of Helium Mixed With Oxygen on the Mechanics of Respiration. J. Clin. Invest., Vol. 15, 1936, p. 47.

249. Barnett, T.B. Effects of Helium and Oxygen Mixtures on Pulmonary Mechanics During Airway Constriction. J. Apply. Physiol., Vol. 22, 1967, pp. 707-713.

250. Bartek, M.J., F. Ulvedal, and H.E. Brown. Study of Man During a 56-day Exposure to an Oxygen-helium Atmosphere at 258 mm Hg Total Pressure. Aerosp. Med., Vol. 37, 1966, pp. 563-566.

251. Bartels, H., and E. Witzleb. Der Einfluss des arteriellen CO_2-druckes auf die chemoreceptorischen Aktionspotenitale im Carotissinusnerven. (Influence of the Arterial CO_2 Pressure on the Chemical-reception Potentials in Carotic Sinus Nerves. Pflüg, Arch., Vol. 262, 1956, pp. 466-472.

252. Bartlett, R.G., and R.A. Hertz. Is it Possible to Differentiate by Inhalation Between Air and Oxygen? Aerosp. Med., Vol. 33, 1962, pp. 552-556.

253. Beck, R.C., J.L. Self, and D.J. Carter. Sucrose Preference Thresholds for Satiated and Water-deprived Rats. Psychol. Rep., Vol 16, 1965, pp. 901-905.

254. Beckaert, J., and I. Leusen. Au sujet de l'influence respiratoire de l'injection soub-occipitale de lobéline. (The Respiratory Influence of Sub-occipital Lobular Injection on Humans.) Schweiz. Med. Wschr., Vol. 86, 1950, p. 1263.

255. Becker-Freuseng, H., and H.G. Clamann. Die Wirkung langdauerneder Sauerstoffatmung in verschiedenen Höhen auf den Menschen. (Effect of Long-duration Oxygen Respiration at Various Altitudes.) Luftfahrtmed, Vol. 7, 1942, pp. 272-291.

256. Behnke, A.R., F.C. Johnson, J.R. Poppen, and E.R. Motley. The Effect of Oxygen on Man at Pressures from 1 to 4 atm. Amer. J. Physiol., Vol. 110, 1935, pp. 565-570.

257. Behnke, A.R., and O.D. Yarbrough. Respiratory Resistance, Oil-water Solubility and Mental Effects of Argon, Compared with Helium and Nitrogen. Amer. J. Physiol., Vol. 126, 1939, pp. 403-415.

258. Belkin, D.A. Aquatic Respiration and Underwater Survival of Two Freshwater Turtle Species. Respirat. Physiol., Vol. 4, 1968, pp. 1-14.

259. Berger, H. Über das Elecktroenkephalogramm den Menschen. (Electroencephalograms in Humans), Arch. Psychiatr. Nerwenkr., Vol. 102, 1934, pp. 537-538.

260. Bergofsky, E.H., and P. Bertun. Response of Regional Circulations to Hyperoxia. J. Apply. Physiol, Vol. 21, 1966, pp. 567-572.

261. Bernards, J.A., P. Dejours, and A. Lacaisse. Ventilatory Effects in Man of Breathing Succesively CO_2-free, CO_2-enriched, and CO_2-free Gas Mixtures with Low, Normal, and High Oxygen Concentration. Respirat. Physiol., Vol. 1, 1966, pp. 390-397.

262. Bernthal, T.G. Respiration. Ann. Rev. Physiol., Vol. 6, 1944, pp. 155-194.

263. Bernthal, T., and W.F. Weeks. Respiratory and Vasomotor Effects of Variations in Carotid Body Temperature. Amer. J. Physiol., Vol. 127, 1939, p. 94.

264. Bert, P. La pression baromètrique (Barometric Pressure), Paris, 1878.

265. Besson, P., P. Dejours, and Y. Laporte. Effets ventilatoires réflexes de la stimulation de fibers afférentes de grand diamétre o'origine musculaire, chez le chat, (Ventilatory Reflexes of the Stimulation of Large-diameter Afferent Fibers in Cat Muscles). Compt. Rend. Soc. Biol., Vol. 153, 1959, pp. 477-481.

266. Biget, P.L., J. Fabre, and F. Violette. Etude des variations de l'excitabilité des centre respiratoires chez le conbaye au ours de l'acclimatement à une altitude moyenne. (Study of Excitability Variations of Respiration Centers During Acclimatization to Medium Altitudes). Compt. Rend. Soc. Biol., Vol. 159, 1965, pp. 312-315.

267. Binet, L., and M. Bochet. Oxygénothérapie (Oxygen Therapy), Paris, 1955.

268. Bishai, H.M. The Effect of Gas Content of Water on Larval and Young Fish. Zschr. Wiss. Zool., Vol. 163, 1960, pp. 37-64.

269. Bishop, J.M., and R.B. Cole. The Effects of Inspired oxygen concentration, age and body position upon the alveolar-arterial Oxygen Tension and Phsyiological Dead Space. J. Physiol., London, Vol. 162, 1962, pp. 60-61.

270. Bjurstedt, H., and M. Hesser. Die Einwirkung von Blutdrucksänderungen im Carotissinus auf die Atmung bei der Katze. (Effect of Blood Pressure Change on Respiration in the Carotic Sinus in Cats), Acta Physiol. Scand., Vol. 4, 1942, pp. 5-12.

271. Bond, G.F. Prolonged Exposure to High Ambient Pressure. Publ. Nat. Acad. Sci.-Nat. Res. Council, Vol. 1181, 1963, pp. 29-34.

272. Bonura, M.S., R.E. Snyder, and W.J. White. Thermal Comfort Zones for Helium-oxygen Atmospheres at Reduced Pressures. Aerosp. Med., Vol. 38, 1967, pp. 912-916.

273. Bonvallet, M., A. Hugelin, and P. Dell. Milieu intérieur et activité automatiques des cellules réticulaires mésencéphaliques (Interior Conditions and Automatic Functioning of Reticular Inesencephalic Cells). J. Physiol., Paris, Vol. 48, 1956, pp. 403-406.

274. Bouverot, P., R. Flandois, and R. Grandpierre. A propos du méchanisme d'action chemoréflexe ou central du "stimulus CO_2" de la ventilation. (The Chemical Reflex of Central Action of the "CO_2 Stimulus" on Ventilation. Comp. Rend. Acad. Sci., Paris, Vol. 252, 1961, pp. 790-792.

275. Bouverot, P., R. Flandrois, R. Puccinelli, and P. Dejours. Etude du rôle des chémoréceteurs artériels dans le régulation de la respiration pulmonaire chez le chien éveillé (Study of the Role of Arterial Chemical Receptors in the Regulation of Pulmonary Respiration in Old Dogs). Arch.Int.Pharmacodyn.Ther., Vol. 157, 1965, pp. 253-281.

276. Bouerverot, P., R. Puccinelli, R. Flandrois, and E. Papiernik. Méchanismus d'action du stimulus CO_2 de la respiration au cours des hypercapnies prolongées (The Mechanism of the CO_2 Stimulus of Respiration During Prolonged Hypercapnia). J. Physiol., Paris, Vol. 55, 1963, pp. 207-208.

277. Bowers, R.W., and E.L. Fox. Metabolic and Thermal Responses of Man in Various He-O_2 and Air Environments. J. Appl. Physiol., Vol. 23, 1967, pp. 561-565.

278. Boycott, A.E., and C.L. Oakley. Oxygen Poisoning in Rats. J. Path. Bact., Vol. 35, 1932, pp. 468-469.

279. Boyd, J.D. The Infereior Aortico-pulmonary Glomus. Brit. Med. Bull., Vol. 17, 1961, pp. 127-131.

280. Bradley, R.D., and S.J.G. Semple. A Comparison of Certain Acid-base Characteristics of Arterial Blood, Jugular Venous Blood, and Cerebrospinal Fluid in Man, and the Effect on Them of Some Acute and Chronic Acid-base Disturbances. J. Physiol, London, Vol. 160, 1962, pp. 381-386.

281. Bradley, R.D., S.J.G. Semple, and G.T. Spencer. Changes in P_{CO_2} of Cisternal c.s.f. in Man Following Carbon Dioxide Adminstration. J. Physiol., London, Vol. 167, 1963, p. 25.

282. Briggs, A. Physiological Exertion, Fitness, and Breathing. J. Physiol. London, Vol. 54, 1920, pp. 292-298.

283. Brousseles, A., A. Michaud, J.P. Crance, and H. Guide. Action de different mélanges gaseux sur les résistances dynamicques respiratories, au repos, entre une et quarte atmosphères, (The Effect of Various Mixed Gases on the Dynamic Respiratory Resistances at Rest Between 1 and 4 Atmospheres). J. Physiol., Paris, Vol. 58, 1966, pp. 477-483.

284. Bullard, R.W., and J.Z. Snyder. Hypoxic Alteration of Righting Ability and Pain Threshold in Two Mammalian Species. Proc. Soc. Exptl. Biol. Med., Vol. 106, 1961, pp. 341-343.

285. Burrows, B., F.B. Saksana, and C.F. Diener. Carbon Dioxide Tension and Ventilatory Mechanics in Chronic Obstructive Long Disease. Ann. Intern. Med., Vol. 65, 1966, pp. 685-700.

286. Campbell, J.A. Tissue oxygen tension and hemoglobin. J. Physiol. London, Vol. 65, 1928, pp. 3-10.

287. Carlsten, A., B. Folkow, G. Gimby, C. Hamberger, and T. Thulesias. Cardiovascular Effect of Direct Stimulation of the Carotid Sinus Nerve in Man. Acta Physiol. Scand., Vol. 44, 1958, pp. 138-145.

288. Carlyle, L. High Altitude Breathing, Approach, Vol. 8, No. 7, 1963.

289. Carpenter, J.G. The Stabilizing Action of Carbon Dioxide on Peripheral Nerve Fibers on the Neurons of the Medullary Reticular Formation on the Rat. Ann. N.Y. Acad. Sci., Vol. 109, 1963, pp. 481-493.

290. Caspers, H., and E. Schutz. Gleichspannungsveranderungen der Hirnrinde bei Beatmung mit verschiedene O_2-Partialdrucken. (Direct Voltage Changes of the Brain Cortex for Respiration at Various O_2 Partial Pressures), Pflügers Arch., Vol. 278, 1963, pp. 75-84.

291. Chalmers, J.P., P.J. Korner, and S.W. White. The Relative Roles of the Aortic and Carotid Sinus Nerves in the Rabbit in the Control of Respiration and Circulation During Arterial Hypoxia and Hypercapnia. J. Physiol., London, Vol. 188, 1967, pp. 435-450.

292. Chambers, A.H., G. Brewen, H.W. Davenport, and S. Goldschmidt. The Respiratory Responses to Anoxemia of the Normal Unanesthetized Dog and Their Causes. Amer. J. Physiol., Vol. 148, 1947, pp. 392-405.

293. Chapin, J.L. Ventilatory Response to Oxygen Breathing of Individuals Acclimatized to High Altitude. J. Aviat. Med., Vol. 25, 1954, pp. 500-503.

294. Chiodi, H. Respiratory Adaptations to Chronic High Altitude Hypoxia. J. Apply. Physiol., Vol. 10, 1957, pp. 81-87.

295. Chiodi, H. Respiratory Adaptation to High Altitude. In: The Regulation of Human Respiration. Oxford, 1963, pp. 363-378.

296. Cohen, P.J., S.C. Alexander, T.C. Smith, M. Reivich, and H. Wollman. Effects of Hypoxia and Normocarbia on Cerebral Blood Flow and Metabolism in Conscious Man. J. Appl. Physiol, Vol. 23, 1967, pp. 183-189.

297. Colard, M., G.R. Mallié, J. Duvernoy, and P. Bouverot. Etude des mécanismes d'action du stimulus CO_2 de la ventilation chez le lapin éveillé (Study of the CO_2 Stimulus on the Ventilation of Old Rabbits), Comp. Rend. Soc. Biol., Vol. 159, 1965, pp. 200-202.

298. Comroe, J.H.G. The Location and Function of the Chemoreceptors of the Aorta. Amer. J. Physiol., Vol. 127, 1939, pp. 176-191.

299. Comroe, J.H. Central and Reflex Control of Breathing. Anesth. Analg. Curr. Res., Vol. 46, 1967, pp. 367-376.

300. Comroe, J.H., E. Forster, A.B. Dubois, W.A. Briscoe, and E. Carlson. The Lung. Clinical Physiology and Pulmonary Function Tests. Chicago, 1956.

301. Comroe, J.H.G., and C.F. Schmidt. The Part Played by Reflexes from the Carotid Body in the Chemical Regulation of Respiration in the Dog. Amer. J. Physiol., Vol. 121, 1938, pp. 75-97.

302. Comroe, J.H., and C.F. Schmidt. Reflexes from the Limbs as a Factor in the Hyperpnea of Muscular Exercise. Amer. J. Physiol, Vol. 138, 1943, pp. 536-547.

303. Cook, C.D., P.A. Drinker, H.N. Jacobson, H. Levinson, and L.B. Strand. Factors Determining the Increase in Pulmonary Blood Flow on Ventilation of the Foetal Lamb Lung. J. Physiol., London, Vol. 166, 1963, pp. 9-10.

304. Cordier, D., and C. Heymans. Le centre respiratoire (The Respiratory Center), Paris, 1935.

305. Cormack, R.S., D.J. Cunningham, and J.B.L. Gee. The Effect of Carbon Dioxide on the Respiratory Response to Want of Oxygen in Man. Quart. J. Exptl. Physiol., Vol. 42, 1957, pp. 303-319.

306. Cozine, R.A., and S.G. Ngai. Medullary Surface Chemoreceptors and Regulation of Respiration in the Cat. J. Appl. Physiol., Vol. 22, 1967, pp. 117-121.

307. Cross, B.A., and J.A. Silver. Unit Activity in the Hypothalamus and the Sympathetic Response to Hypoxia and Hypercapnia. Exptl. Neurol., Vol. 7, 1963, pp. 375-397.

308. Cross, K.W., and J.L. Malcolm. Evidence of Carotid Body and Sinus Activity in Newborn and Foetal Animals. J. Physiol., London, Vol. 118, 1952, pp. 10-11.

309. Cross, K.W., and T.E. Oppé. The Effect of High and Low Concentrations of Oxygen on the Respiration of the Premature Infant. J. Physiol., London, Vol. 117, 1952, pp. 38-55.

310. Cross, K.W., and P. Warner. The Effect of Inhalation of High and Low Oxygen Concentrations on the Respiration of the Newborn Infant. J. Physiol., London, Vol. 114, 1951, pp. 283-290.

311. Cunningham, D.J.C., D.H. Elliot, B.B. Lloyd, J.P. Miller, and J.M. Young. A Comparison of the Effect of Oscillating and Steady Alveolar Partial Pressure of Oxygen and Carbon Dioxide on the Pulmonary Ventilation. J. Physiol., London, Vol. 179, 1965, pp. 498-508.

312. Cunningham, D.J.C., B.B. Lloyd, and J.M. Patrick. The Respiratory Response of Hypoxic Resting Men to CO_2 "Injected" at Constant Rates into the Inspired Air J. Physiol., London, Vol. 171, 1964, pp. 53-54

313. Cutler, R.G., W.G. Robertson, R.E. McKenzie, F. Ulvedal, J.J. Hargraves, and B.E. Welch. Human Responses to Carbon Dioxide in the Low Pressure Oxygen-rich Atmosphere. Aerosp. Med., Vol. 35, 1964, pp. 317-323.

314. Daly, M. de Burgh, C.J. Lambertsen, and A. Schweitzer. Observations on the Volume of Blood Flow and Oxygen Utilization of the Carotid Body in the Cat. J. Physiol., London, Vol. 125, 1954, pp. 67-69.

315. Dautrebande, L. Les gas toxiques (Toxic Gases)., Paris, 1933.

316. Dawes, G.S., and J.C. Mott. Reflex Respiratory Activity in the Newborn Rabbit. J. Physiol., London, Vol. 145, 1959, pp. 85-97.

317. Dejours, P. Chemoreflexes in Breathing. Physiol. Revs., Vol. 42, 1962, pp. 335-385.

318. —————. Control of Respiration by Arterial Chemoreceptors. Ann. N.Y. Acad. Sci., Vol. 109, 1963, pp. 682-685.

319. Dejours, P., J. Armand, and G. Verriest. Carbon Dioxide Curves of Water and Gas Exchange of Water-breathers. Respirat. Physiol., Vol. 5, 1968, pp. 23-33.

320. Dejours, P., Y. Labrousse, J. Raynaud, F. Gigard, and A. Teillac. Stimulus oxygène de la ventilation au repos et au course de l'exercise musculaire à basse altitude chez l'homme (Oxygen Stimulation of Ventilation at Rest and for Muscular Exercise in Humans at Low Altitudes). Rev. Franc. Etudes Clin. Biol., Vol. 3, 1958, pp. 105-123.

321. Dejours, P., J.C. Mithoefer, and Y. Labrousse. Influence of Local Chemical Change on Ventilatory Stimulus from the Legs During Exercise. J. Appl. Physiol., Vol. 10, 1957, pp. 372-375.

322. Dejours, P., J.C. Mithoefer, and A. Teillac. Essai de mise en évidence de chémorécepteurs veineux de ventilation (Essay on the Existence of venous Chemoreceptors of Ventilation). J. Physiol., Paris, Vol. 47, 1955, pp. 160-163.

323. Dejours, P., R. Puccinelli, J. Armand, and M. Dicharry. Concept and Measurement of Ventilatory Sensitivity to Carbon Dioxide. J. Appl. Physiol., Vol. 20, 1965, pp. 890-897.

324. Diemer, K. Über die Sauerstoffdiffusion im Gehirn (Oxygen Diffusion in the Brain). Pflügers Arch., Vol. 285, 1965, pp. 108-118.

325. Diemer, K., and R. Henn. Kapillarvermehrung in der Hirnrinde der Ratte unter chronischem Sauerstoffmangel (Capillary Multiplication in the Brain Cortex of Rats Due to Chronic Oxygen Insufficiency). Naturwissensch., Vol. 52, 1965, pp. 135-136.

326. Dirken, M.N., and H. Heemstra. The Adaptation of the Lung Circulation to the Ventilation. Quart. J. Exptl. Physiol., Vol. 34, 1947/48, pp. 213-225.

327. Dolezal, V. The Effect of Longlasting Oxygen Inhalation Upon Respiratory Parameters in Man. Physiol. Bohemosl., Vol. 11, 1962, pp. 149-158.

328. Dornhorst, A.C. The Regulation of Breathing. Brit. Med. Bull., Vol. 19, 1963, pp. 4-6.

329. Douglas, J.C., and O.G. Edholm. Measurement of Saturation Time and Saturation Tension with Millikan Oximeter in Subjects with Normal Pulmonary Function. J. Appl. Physiol., Vol. 2, 1949, pp. 307-315.

330. Downes, J.J., and C.J. Lambertsen. Dynamic Characteristic of Ventilatory Depression in Man on Abrupt Administration of Oxygen. J. Appl. Physiol., Vol. 21, 1966, pp. 443-447.

331. Dripps, R.D., and J.H. Comroe. The Effect of the Inhalation of High and Low Oxygen Concentration on Respiration, Pulse Rate, Ballistocardiogram and Arterial Oxygen Saturation of Normal Individuals. Amer. J. Physiol., Vol. 149, 1947, pp. 277-291.

332. Duke, H.N., J.H. Green, and E. Neil. Carotid Chemoreceptor Impulse Activity During Inhalation of Carbon Monoxide Mixtures. J. Physiol., London, Vol. 118, 1952, pp. 520-527.

333. Dumke, P.R., and C.F. Schmidt. Quantitative Measurements of Cerebral Blood Flow in the Macaeque Monkey. Amer. J. Physiol., Vol. 138, 1943, pp. 421-431.

334. Dutton, R.E., V. Chernick, H. Moses, B. Bromberger-Barnea, S. Permutt, and K.L. Riley. Ventilatory Response to Intermitten Inspired Carbon Dioxide. J. Appl. Physiol., Vol. 19, 1964, pp. 931-936.

335. Dutton, R.E. W.A. Hodson, D.G. Davies, and V. Chernick. Ventilatory Adaptation to a Step Change in P_{CO_2} at the Carotid Bodies. J. Appl. Physiol., Vol. 23, 1967, pp. 195-202.

336. Dutton, R.E., Som Nath, and R.L. Riley. Reflex Stimulation of Pulmonary Ventilation by Mixed Venous P_{CO_2}. Federat. Proc., Vol. 19, 1960, p. 382.

337. Egusa, S., and T. Yamamoto. Studies on the Respiration of the "Kuruma" Prawn, *Penaeus japonicus* Bate. Bull. Japan. Soc. Sci. Fish., Vol. 27, 1961, pp. 22-27.

338. Elftman, A.J. Afferent and Parasympathetic Innervation of the Lungs and Trachea in the Dog. Amer. J. Physiol., Vol. 72, 1943, pp. 1-28.

339. Ellis, M.M. Respiratory Volumes of Men During Short Exposures to Constant Low Oxygen Tensions Attained by Rebreathing. Amer. J. Physiol., Vol. 50, 1919, pp. 267-279.

340. Epperson, W.L., D.G. Quigley, W.G. Robertson, V.S. Behar, and B.E. Welch. Heat Exchange During Exercise in a Helium-oxygen Atmosphere. Aerosp. Med., Vol. 36, 1965, pp. 143-148.

341. —————————————————. Observations on Man in an Oxygen-helium Environment at 380 mm Hg Total Pressure. Aerosp. Med., Vol. 37, 1966, pp. 457-462.

342. Euler, C., and U. Söderberg. Medullary Chemosensitive Receptors. J. Physiol., London, Vol. 118, 1952, pp. 545-550.

343. Euler, U.S., and G. Liljestrand. The Effect of Carotid Sinus Denervation on Respiration During Rest. Acta Physiol. Scand., Vol. 1, 1940/41, pp. 93-104.

344 Euler, U.S., H. Liljestrand, and Y. Zotterman. The Excitation Mechanism of the Chemoreceptors of the Carotid Body. Scand. Arch. Physiol., Vol. 83, 1939, pp. 132-152.

345. Eyzaguirre, C., and H. Koyano. Effects of Hypoxia, Hypercania, and pH on the Chemoreceptor Activity of the Carotid Body in Vitro. J. Physiol., London, Vol. 178, 1965, pp. 385-409.

346. Ezyzaguirre, C., and J. Lewin. Effect of Different Oxygen Tensions on the Carotid Body in Vitro. J. Physiol., London, Vol. 159, 1961, pp. 238-250.

347. Fallis, A.M., and S.M. Smith. Ether Extracts from Birds and CO_2 as Attractants for Some Ornitophilic Simuliids. Canad. J. Zool., Vol. 42, 1964, pp. 723-730.

348. Fenn, W.O., H. Rahn, and A.B. Otis. A Theoretical Study of the Composition of Alveolar Air at Altitude. Amer. J. Physiol., Vol. 146, 1946, pp. 637-653.

349. Finkelstein, S., J.F. Tomashefski, and F.H. Shillito. Pulmonary Mechanics at Altitude in Normal and Obstructive, Lung Disease Patients. Aerosp. Med., Vol. 36, 1965, pp. 880-884.

350. Fitzgerald, R.S., J.F. Zaitchuk, R.W. Penman, and J.F. Parkins. Ventilatory Response to Transient Perfusion of Carotid Chemoreceptors. Amer. J. Physiol., Vol. 207, 1964, pp. 1305-1313.

351. Flenley, D.C. The Changes in the Rate of Human Inspiratory Work Produced by Alterations in the Arterial Blood Gas Tension and pH. Quart. J. Exptl. Physiol., Vol. 49, 1964, pp. 446-484.

352. Florez, J., and H.L. Borison. Tidal Volume in CO_2 Regulation: Peripheral Denervations and Ablation of Area Postrema. Amer. J. Physiol., Vol. 212, 1967, pp. 985-991.

353. Floyd, W.F., and E. Neil. The Influence of the Sympathetic Innervation of the Carotid Bifurcation on the Chemoreceptor and Baroreceptor Activity in the Cat. Arch. Intern. Pharmacodyn., Vol. 91, 1952, pp. 230-239.

354. Fowler, K.T., and J. Read. Effect of Alveolar Hypoxia on Zonal Distribution of Pulmonary Blood Flow. J. Appl. Physiol., Vol. 18, 1963, pp. 244-250.

355. Fowler, W.S. Breaking Point of Breath-holding. J. Appl. Physiol., Vol. 6, 1954, pp. 539-545.

356. Fox, E.L., H.S. Weiss, R.L. Bartels, and E.P. Hiatt. Thermal Responses of Man During Rest and Exercise in a Helium and Oxygen Environment. Arch. Environm. Health, Vol. 13, 1966, pp. 23-28.

357. Fuleihan, F.J.D., T. Nakamura, J.T. Suero, D.S. Merrifield, and R.L. Riley. Ventilatory Changes During Transient States of CO_2 Breathing. Federat. Proc., Vol. 21, 1962, p. 449.

358. Garbinski, T. Choroby narzadu oddechowego (Diseases of the Respiratory System). 1967, Warsaw.

359. Garcia, J., D.J. Kimeldorf, and R.A. Koelling. Conditioned Aversion to Saccharin Resulting from Exposure to Gamma Radiation. Science, Vol. 122, 1955, pp. 157-158.

360. Gaudebount, G.J., J.J. Pocidalo, C. Poyart, and M.C. Blayo. Effets de l'hyperoxie sanguine sur l'oxygène du liquide céphalorhacidien cisternal du chien. (Effects of Hyperoxic Fluid on the Oxygen in the Cephalorhachidian Cisternal Liquid of Dogs). Compt. Rend. Séances. Soc. Biol. Ses. Filiales, Vol. 159, 1965, pp. 1926-1929.

361. Gemill, C.L., and D.L. Reeves. The Effects of Anoxemia in Normal Doses Before and After Denervation of the Carotid Sinuses. Amer. J. Physiol., Vol. 105, 1933, pp. 487-495.

362. Gesell, R. Regulation der Atmung und des Kreislaufs (Regulation of Breathing and the Circulatory System). Ergebn. Physiol., Vol. 28, 1929, pp. 340-442.

363. ——————. Respiration and its Adjustments. Ann. Rev. Physiol., Vol. 1, 1939, pp. 185-216.

364. Gesell, R., J. Lapides, and M. Levin. The Interaction of Central and Peripheral Chemical Control of Breathing. Amer. J. Physiol., Vol. 130, 1940, pp. 155-169.

365. Gesell, R., and C. Moyer. Is Breathing Fundamentally a Reflex Phenomenon? Quart. J. Physiol., Vol. 25, 1935, pp. 13-27.

366. Gilbert, D.L. The Interdependence Between the Biosphere and the Atmosphere. Respirat. Physiol., Vol. 5, 1968, pp. 68-77.

367. Girard, F., A. Teillac, R. Lefracois, and A. Lacaisse. Etude du stimulus oxygène de la ventilation en hypoxie aiguë. (Study of the Oxygen Stimulus on Ventilation for Pronounced Hypoxia). J. Physiol., Paris, Vol. 51, 1959, pp. 469-470.

368. Gleason, T.L., and R.H. Edwards. Physiological Tolerance Study of Chimpanzees Breathing 100% Oxygen at 5 psi. Biol. Abstr., Vol. 47, 1963, No. 15353.

369. Grafe, B., E. Chanin, and J. Tylor. The effect of helium and oxygen mixtures on pulmonary resistances in emphysema. Amer. J. Respir. Dis., Vol. 81, 1960, p. 823.

370. Grandpierre, R., G. Neverre, J. Rozier, and P. Faltot. Activité unitaire réticulaire et variations de Pa_{CO_2} et de Pa_{O_2} enregistrées de facon continue chez le lapin (Reticular Unit Activities and Variations of P_{CO_2} and P_{O_2} in Rabbits Recorded in a Continuous Fashion). J. Physiol., Paris, Vol. 59, 1967, pp. 420-421.

371. Grant, W.C. Influence of carotid body removal on polycythemia and arterial oxygen saturation during discontinuous anoxia. Amer. J. Physiol., Vol. 164, 1951, pp. 224-230.

372. Gray, F.D., and A.S. Field. The use of mechanical assistance in treating cardiopulmonary diseases. Amer. J. Med. Sci., Vol. 238, 1959, pp. 146-154.

373. Gray, J.S. Pulmonary ventilation and its physiological regulation. Amer. Lecture Series 63, Springfield, 1950.

374. Green, R., and B. Day. Preoperative administration of helium in respiratory obstruction. Lancet, Vol. 246, 1954, p. 603.

375. Greenfield, L.H., and P.A. Ebert. Cardiac denervation effect in hypoxia and hypercapnia. Arch. Surg., Vol. 87, 1963, pp. 717-721.

376. Grodins, F.S. Regulation of pulmonary ventilation. Physiologist, Vol. 7, 1964, pp. 319-333.

377. Grodins, F.S., J.S. Gray, K.R. Schroeder, A. L. Norins, and R.W. Jones. Respiratory responses to CO_2 inhalation. J. Appl. Physiol., Vol. 7, 1954, pp. 283-308.

378. Guz, A., M.J.M. Noble, J.G. Widdicombe, D. Trenchard, and W.W. Muchin. Peripheral chemoreceptor block in man. Respirat. Physiol., Vol. 1, 1966, pp. 38-40.

379. ————————————————————. The effect of bilateral block of vagus and glossopharyngeal nerves on the ventilatory response to CO_2 of conscious man. Respirat. Physiol., Vol. 1, 1966, pp. 206-207.

380. Haldane, J.C., and J.G. Priestley. Respiration. Oxford, 1935.

381. Hall, F.G. Minimal utilizable oxygen and the oxygen dissociation curve of blood of rodents. J. Appl. Physiol., Vol. 21, 1966, pp. 375-378.

382. Hamilton, R.W., J.B. MacInnis, L.A. Trovato, and H.R. Schreiner. Biological effects of helium on man and results of a multi-day exposure to this gas at 20 atm. Aerosp. Med., Vol. 37, 1966, pp. 281-288.

383. Hanks, E.S., S.H. Ngai, and B.R. Fink. The respiratory threshold for carbon dioxide in anesthetized man. Anesthesiol., Vol. 22, 1961, pp. 393-397.

384. Harned, H.S., C. Griffin, W.S. Berryhill, L.C.MacKinney, and K. Sugioka. Role of carotid chemoreceptors in the initiation of effective breathing of the lamb at term. Pediatrics, Vol. 39, 1967, pp. 329-336.

385. Hashisuka, H. Studies on the mechanism of hyperventilation in muscular exercise. J. Physiol. Soc. Japan., Vol. 27, 1965, pp. 325-334.

386. Heck, E., and H.H. Löschcke. Wirkung hoher Sauerstoffteildrucke auf die Atmung (Effect of increased oxygen partial pressures on respiration). Luftfahrtmed., Vol. 6, 1942, pp. 114-118.

387. Hegedus, S.A., and R.S. Shackelford. Carbon dioxide and obstructed cerebral blood flow. J. Amer. Med. Assoc., Vol. 191, 1965, pp. 279-282.

388. Heisey, S.R., D. Held, and V. Fense. The role of cerebrospinal fluid in respiratory responses to CO_2 in unanesthetized goats. Federat. Proc., Vol. 23, 1964, p. 258.

389. Heller, M.L., and T.R. Watson. Arterial oxygenation during transition from 100% oxygen to air breathing: Polarographic P_{CO_2} study. Anesthesiol., Vol. 22, 1961, pp. 385-392.

390. Hering, H.E. Der Karotisdruckversuch (The Carotid Pressure Experiment). Münch. Med. Wschr., Vol. 42, 1923, p. 1987.

391. Herter, K. Untersuchungen über den Temperatursinn einiger Insecten (Investigations on the temperature sensitivity of several insects). Zschr. Vergl. Physiol., Vol. 1, 1924, pp. 221-234.

392. ——————— Eine verbesserte Temperaturorgel und ihre Anwendung an Insecten und Säugetiere (An improved temperature organ and its application to insects and mammals). Biol. Zentralbl., Vol. 54, 1934, pp. 487-501.

393. ——————— Das thermotaktische Optimum bei Nagetieren — ein mendelndes Art-und Rassenmerkmal (The thermotactic optimum for rodents, a type and race characteristic). Zschr. Vergl. Physiol., Vol. 23, 1936, pp. 605-614.

394. Hesser, C.M. Central and chemoreflex components in the respiratory activity during acid-base displacement in the blood. Acta Physiol. Scand., Vol. 18, Suppl. 64, 1949.

395. Hesser, C.M., and G. Mattel. The alveolar-arterial O_2 difference during light and moderate exercise in man. Abstr. XI Scand. Physiol. Congr. Copenhagen, 1963, p. 66.

396. Heymans, C. Sensory and reflexogenic vascular zones of the aorta and carotid sinus, and their importance in physiology, pathology, and pharmacology. Uspekhi Sovremmenoy biologii, Vol. 3, No. 3, 1934, pp. 362-372.

397. ——————— Baroceptor and chemoceptor reflexes in monkeys. Circulat. Res., Vol. 6, 1958, pp. 567-569.

398. ——————— and J.J. Bouckaert. Sinus carotidiens et réflexes respiratoires (Sinus Carotids and Respiratory Reflexes). Compt. Rend. Soc. Biol., Vol. 103, 1930, pp. 498-500.

399. Heymans, C., J. Bouckaert, and L. Doutrebande. Sinus carotidien et réflexes respiratoires (Sinus Carotids and Respiratory Reflexes). Arch. Intern. Pharmocodyn., Vol. 40, 1932, pp. 54-70.

400. Heymans, C., and E. Neil. Reflexogenic areas of the cardiovascular system. London, 1958.

401. Heymans, C., G.R. Vleeschhouver, and A.F. Schaepdryver. Liquide céphalorochidien stimulation de la respiration par le CO_2 (Cephalorhachidian Liquid Simulation of Respiration by CO_2). J. Physiol., Paris, Vol. 57, 1965, pp. 627-628.

402. Heymans, J.F., and C. Heymans. Sur la régulation reflexe de la respiration (On the Regulation Reflex of Respiration). Ann. Physiol., Vol. 3, 1927, pp. 471-473.

403. Honda, Y. Ventilatory response to CO_2 during hypoxia and hyperoxia in awake and anesthetized rabbits. Respirat. Physiol., Vol. 5, 1968, pp. 279-287.

404. Honda, Y., and F. Kreuzer. P_{O_2}-ventilation response curve with normal pH and P_{CO_2} in the dog. J. Appl. Physiol., Vol. 21, 1966, pp. 423-433.

405. Honda , Y., T. Natsui, and N. Hasumura. Analysis of ventilatory response to CO_2 during hypoxia in dogs. J. Appl. Physiol., Vol. 20, 1965, pp. 839-843.

406. Honda, Y., T. Natsui, N. Hasumura, and K. Nakamura. Threshold P_{CO_2} for respiratory system in acute hypoxia in dogs. J. Appl. Physiol., Vol. 18, 1963, pp. 1053-1056.

407. Hornbein, T.F., Z.J. Griffo, and A. Roos. Quantitation of chemoreceptor activity: Interrelation of hypoxia and hypercapnia. J. Neurophysiol., Vol. 24, 1961, pp. 561-568.

408. Hornbein, T.F., and A. Roos. Effect of mild hypoxia on ventilation during exercise. J. Appl. Physiol., Vol. 17, 1962, pp. 239-242.

409. Horner, P.L. The role of the arterial chemoreceptors and baroreceptors in the circulatory responses to hypoxia of the rabbit. J. Physiol., London, Vol. 180, 1965, pp. 279-303.

410. Hortolomei, N., G. Proca, J. Busu, J.N. Enescu, and N. Hasnas. Le role des voies respiratoires inferieures dans la regulation de la Respiration (The Role of Lower Respiratory Tracts in the Regulation of respiration). Bull. Sci., Sect. Sci. Med., Vol. 5, 1963, p. 641.

411. Hostetler, T., and R.G. Manning. Changes is blood carbon dioxide tension with inhalation of 10% carbon dioxide in oxygen. Amer. J. Med. Sci., Vol. 248, 1964, pp. 429-433.

412. Howard, P., and R.W.B. Penman. The effect of breathing 30% oxygen on pulmonary ventilation-perfusion inequality in normal subjects and patients with chronic lung disease. Clin. Sci., Vol. 32, 1967, pp. 127-137.

413. Hughes, G.M., and G. Shelton. Respiratory mechanisms and their nervous control in fish. In: Advances in Comp. Physiol. Biochem., N.Y., Vol. 1, 1962, pp. 275-361.

414. Hurtado, A. Acclimatization to high altitudes. In: The Physiological Effects of High Altitudes. Oxford, London, N.Y., Paris, 1964 pp. 1-15.

415. Hyde, R.W., W.H. Lawson, and R.E. Forster. Influence of carbon dioxide on pulmonary vasculature. J. Appl. Physiol., Vol. 19, 1964, pp. 734-744.

416. Iaria, C.F., U.J. Jalar, and F.F. Cao. The peripheral neural mechanism of exercise hyperpnea. J. Physiol., London, Vol. 148, 1959, pp. 49-40.

417. Jacobson, J., A.M. Harper, and D.C. McDowall. The effect of oxygen under pressure on cerebral blood-flow and cerebral venous oxygen tension. Lancet, No. 7307, 1963, p. 549.

418. Jesse, M.J., C. Shub, and A.P. Fishman. Lung and hill ventilation of of the African lung fish. Respirat.Physiol., Vol. 3, 1967, pp. 267-287.

419. Joels, N., and E. Neil. Chemorectpor impulse activity evoked by perfusion of the glomus at various P_{CO_2} and pH values. J. Physiol., London, Vol. 154, 1960, p. 7.

420. ————————————— Carotid glomus chemosensory excitation. J. Physiol., London, Vol. 164, 1962, pp. 11-12.

421. Kane, H. The use of helium and oxygen in the treatment of asphyxia neonatorum. Amer. J. Obst. Gyn., Vol. 40, 1940, pp. 140-149.

422. Kao, F.F., C.C. Michel, S.S. Mei, and W. K. Li. Somatic afferent influence on respiration. Ann. N.Y. Acad. Sci., Vol. 109, 1963, pp. 969-700.

423. Katsaros, B. Die Rolle der Chemoreceptoren des Carotisgebietes der narkotisierten Katz für die Antwort der Atmung auf isolierte Änderungen der Wassertoffionen-Konzentration und des CO_2-Drucks der Blutes

(The role of chemoreceptors of the Carotid Region of Anesthetized Cats in the Breathing Response to Isolated Changes of the Helium Ion Concentration and the CO_2 Pressure of the Blood). Pflüg. Arch., Vol. 282, 1965, pp. 157-178.

424. Katsares, B., and H.H. Loeschcke. Über den Beitrag der Chemoreceptoren des Carotisgebietes zum Anteil der Lungenventilation durch Wasserstoffionen und CO_2 bein hohem O_2-Druck. (The Contribution of the Chemoreceptors of the Carotid Region to the Lung Ventilation by Hydrogen Ions and CO_2 for Increased O_2 Pressure). Naturwissenschaft, Vol. 51, 1964, pp. 270-285.

425. Katz, R.L., S.H. Ngai, G.G. Nahas, and S.G. Wang. Relationship between acid-base balance and the central respiratory mechanism. Amer. J. Physiol., Vol. 204, 1963, pp. 867-872.

426. Keller, C.H., and A. Loeser. Der zentripetale Lungenvagus (The Centripetal Lung Vagus). Zschr. Biol., Vol. 89, 1930, pp. 373-395.

427. Kety, S.S. Circulation and metabolism of the human brain in health and disease. Amer. J. Med., Vol. 8, 1948, pp. 205-217.

428. Kirchoff, H.W. Examens combinés de la circulation et de la respiration sous diverses concentrations d'oxygène (Combined Examinations of Circulation and Respiration for Various Oxygen Concentrations). Rev. Méd. Aéronaut., Vol. 2, 1963, pp. 463-466.

429. Klinger, J. Die Orientierung von *Ditylenchus dipsai* in gemessenen künslichen und biologischen CO_2-Gradienten (The Orientation of *Ditylenchus dipsai* in Measured Artificial and Biological CO_2 Gradients). Nematol., Vol. 9, 1963, pp. 185-199.

430. Klinger, J. Über de Sitz der CO_2-Receptoren bei der Larve von
     Otiorynchus sulcatus (The Location of the CO_2 Receptors in the Larvae
     of *Otiorynchus sulcatus*). Entomol. Exptl. Appl., Vol. 9, 1966,
     pp. 271-277.

431. Knowles, J.H. Respiratory physiology and its clinical application.
     Cambridge, Mass., 1959.

432. Koch, E. Die reflektorische Selbststeuerung des Kreislaufes (The
     Reflected Self-control of the Circulatory System). Leipzig, 1931.

433. Krage, V.E. The glomus pulmonale: Its location and microscopic anatomy.
     In: Ciba Foundation Symposium on pulmonary structure and function.
     London, 1962, pp. 53-76.

434. Krogh, A.   The comparative physiology of respiratory mechanisms.
     Philadelphia, 1959.

435. Lamb, T.M.   Ventilatory responses to intravenous and inspired carbon
     dioxide in anesthetized cats. Respirat. Physiol., Vol. 2, 1966/67,
     pp. 99-104.

436 Lambertsen, C.J. The philosophy of extremes for the gaseous environ-
     ment of manned, closed ecological systems. Aerosp. Med., Vol. 34,
     1963, pp. 291-299.

437. ────────────── Physiological effects of oxygen. Publ. Nat. Acad.
     Sci. - Nat. Res. Council, No. 1181, 1963, pp. 171-187.

438. Lambertsen, C.J., P. Hall, H. Wollman, and M. Goodman. Quantitative
     interactions of increased P_{O_2} and P_{CO_2} upon respiration in man. Ann.
     N.Y. Acad. Sci., Vol. 109, 1963, pp. 731-472.

439. Lambertsen, C.J., R.H. Kough, D.L. Emmel, H.H. Loeschcke, and
     C.F. Schmidt. Comparison of relationship of respiratory minute volume
     to P_{CO_2} and pH of arterial and internal jugular blood in normal man
     during hyperventilation produced by low concentrations of CO_2 at 1 atm
     and low O_2 at 3 atm. J. Appl. Physiol., Vol. 5, 1953, pp. 803-814.

440. Lambertsen, C.J., H. Wollman, and R. Gelfand. The dynamics of change in
     respiration and arterial blood and CSF acid-base parameters during ad-
     ministration and withdrawal of CO_2. Feder. Proc., Vol. 20, 1961,
     p. 430.

441. Landgren, S., and Y. Zotterman. The recording of chemoreceptive spike
     activity in dogs. Acta Physiol. Scand., Vol. 22, 1951, pp. 79-82.

442. Lanphier, E.H. Nitrogen-oxygen mixture physiologie. Nav. Exptl. Diving
       Unit Res. Rept., 1958, pp. 7-58.

443. Larsell, O. The ganglia plexus and nerve termination of the mammalia
       lung and pleura pulmonalis. J. Compar. Neurol, Vol. 34, 1922,
       pp. 97-131.

444. Lefrancois, R., H. Gautier, P. Pasquis, and J. Leroy. Comparaison entre
       les résponses ventilatoires au stimulus oxygène au cours des hypoxies
       aiguë et chronique (Comparison of the ventilatory responses to oxygen
       stimulation during increased and chronic hypoxia). J. Physiol., Paris,
       Vol. 58, 1966, pp. 245-254.

445. Left, H.J., J. Lester, and G.J. Motsay. Study of man during a 56-day
       exposure to an oxygen-helium atmosphere at 258 mm Hg total pressure.
       Aerosp. Med., Vol. 37, 1966, pp. 601-604.

446. Lehman, G., and O. Graf. Versuche über die Wirkung von Sauerstoffatmung
       bei normalen Druck auf die Leistungfäigkeit (Experiments on the effect
       of oxygen respiration on productivity for normal pressures).
       Luftfahrmed., Vol. 6, 1942, pp. 183-200.

447. Leitner, L.M., B. Pages, R. Puccinelli, and P. Dejours. Etude simultanee
       de la ventilation et de decharges des chemorecepteurs du glomus
       carotidien chez le chat (Simultaneous study of ventilation and chemo-
       receptor discharges of the carotic glomus in cats). Arch. Intern.
       Pharmocodyn., Vol. 154, 1965, pp. 427-433.

448. Lenfant, C. Effect of high Fi_{O_2} on measurement of ventilation-perfusion
       distribution in man at sea level. Ann. N.Y. Acad. Sci., Vol. 121,
       1965, pp. 797-808.

449. Leon, H.A., and S.F. Cook. A mechanism by which helium increases metabo-
       lism in small mammals. Amer. J. Physiol., Vol. 199, 1960,
       pp. 243-245.

450. Levine, B.E., B. Bigelow, and R.D. Hamstra. The role of long-term con-
       tinuous oxygen administration in patients with chronic airway obstruc-
       tion with hypoxemia. Ann. Intern. Med., Vol. 66, 1967, pp. 639-650.

451. Linde, L.M., D.H. Simmons, N.A. Lewis, and R. Powell. The effect of CO_2
       breathing on pulmonary and systemic hemodynamics. Amer. J. Dis. Child.,
       Vol. 102, 1961, pp. 551-552.

452. Lloyd, B.B., M.G. Jukes, and D.J. Cunningham. The relation between
       alveolar oxygen pressure and the respiratory response to carbon dioxide
       in man. Quart. J. Exptl. Physiol., Vol. 43, 1958, pp. 214-227.

453. Loeschcke, H.H. Beziehungen zwischen CO_2 und Atmung (Relationships be- CO_2 and respiration). Anaesthesist., Vol. 9, 1960, pp. 38-46.

454. ─────────── A concept of the role of intracranial chemosensitivity in respiratory control. In: Cerebrospinal fluid and regulation of ventilation. Oxford, 1965, pp. 183-207.

455. Loeschcke, H.H., and H.H. Gertz. Einfluss des O_2-Druckes in der Einatmungsluft auf die Atemtätgkeit des Menschen, gepruft unter Konstanthaltung des alveolaren CO_2-Druckes (Influence of the CO_2 pressure in inhaled air on the respiration of humans, tested while maintaining constant alveolar CO_2 pressure). Pflügers Arch., Vol. 267, 1958, pp. 460-477.

456. Loeschcke, H.H., and H.P. Koepchen. Wirkungen von Wasserstoffionen und CO_2 im Liquor cerebrospinalis auf die Atmung (Effects of hydrogen ions and CO_2 in the cerebrospinal fluid on respiration). Pflügers Arch., vol. 266, 1957, pp. 9-17.

457. ─────────── Über das Verhalten der Atmung und des arteriellen Drucks bei einbringen von Veratridin, Lobelin und Cyanid in den Liquor cerbrospinalis (The respiration and arterial pressure behavior when veratridine, lobeline, and cyanide are intro- duced into the cerebrospinal fluid). Pflügers Arch., Vol. 266, 1958, pp. 589-610.

458. Loeschcke, H.H., H.P. Koepchen, and K.H.N. Gertz. Über den Einfluss von Wasserstoffionenkonzentration und CO_2-Druck im Liquor cerebrospinalis auf die Atmung (The influence of hydrogen concentration and CO_2 pressure in the cerebrospinal fluid on respiration). Pflügers Arch., Vol. 266, 1958, pp. 569-585.

459. Loeschcke, H.H., R.A. Mitchell, and B. Katsaros. Interation of intra- cranial chemosensitivity with peripheral afferents to the respiratory centers. Ann. N.Y. Acad. Sci., Vol. 109, 1963, pp. 651-650.

460. Lutz, B.R., and E.C. Schneider. The reactions of the cardiac and respir- atory centers to changes in oxygen tension Amer. J. Physiol., Vol. 50, 1919, pp. 327-341.

461. Lyszczarz, J., and M. Glogowska. Effect of the composition of atmospher- ic air on respiratory function. Acta Physiol. Polon., Vol. 17, 1966, pp. 795-802.

462. Madarasz, J., F.Obal, M. Viczay, and O. Takas. Analysis of the vegeta- tive and EEG responses to hypoxia. Acta Physiol. Acad. Sci. Hung., Vol. 28, 1965, pp. 77-88.

463. Maio, D.A., and L.F. Fahri. Effect of gas density on mechanics of breathing. J. Apply. Physiol., Vol. 23, 1967, pp. 687-693.

464. Mallie-Colard, M., J.P. Mallie, and P. Bouverot. Rôles des afférances chimiosensibles d'origine artérielle dans la régulation, de la ventilation (The role of chemical affinity of the arteries on regulation of ventilation). Ann. Sci. Univ. Besancon Med., Vol. 1, 1965, pp. 3-14.

465. Malmejac, J., M. Rieu, F. Clostre, and M Schlotterer. Méchanisme du réinforcement de l'excitabilité des centres respiratoires au CO_2 sous l'influence d'une faible hypoxie (Reinforcement mechanism of the respiratory center excitability with respect to CO_2 under the influence of weak hypoxia). Compt. Rend. Soc. Biol., Vol. 160, 1966, pp. '486-490.

466. Malmejac, J., M. Rieu, and M. Schlotterer. Sur le role de l'equilibre CO_2-O_2 dans la regulation des mouvements respiratoires (The role of the CO_2-O_2 equilibrium in the regulation of respiratory movements). J. Physiol., Paris, Vol. 58, 1966, pp. 567-573.

467. Manley, E.S., C.B. Nash, and R.A. Woodbury. Cardiovascular responses to severe hypercapnia of short duration. Amer. J. Physiol., Vol. 207, 1964, pp. 634-640.

468. Margaria, R. Une representation convenable de plusieurs caractres fonctionnels significatifs (A practical representation of several significant functional characteristics). J. Physiol., Paris, Vol. 57, 1965, pp. 653-654.

469. Marks, B.H., A.N. Bhattacharya, and J. Vernikos-Nannelis. Effect of hypoxia on secretion of ACTH in the rat. Amer. J. Physiol, Vol. 208, 1965, pp. 1021-1025.

470. Marshall, L.D., E.N. Lanphier, and A.B. Dubois. Resistance to breathing in normal subjects during simulated dives. J. Apply. Physiol., Vol. 9, 1956, pp. 5-10.

471. Masland, W.S., and W.S. Yamamotor. Abolition of ventilatory response to inhaled CO_2 by neurological lesions. Amer. J. Physiol., Vol. 203, 1962, pp. 789-795.

472. Matell, G. Time-courses of changes in ventilation and arterial gas tensions in man induced by moderate exercise. Acta Physiol. Scand., Vol. 58, Suppl. 206, 1963.

473. Mattes, K., Q.J. Gilbert, and X. Malikiosis. Über das Verhalten des arteriellen O_2-Sättigung bei hohem alveolaren O_2-Spannungen (The behavior of arterial O_2 saturation for increased O_2 tensions). Arch. Exptl. Pathol. Pharmac., Vol. 185, 1937, pp. 622-630.

474. McDowall, D.G. Hyperbaric oxygen in relation to circulatory and respiratory emergenices. Brit. J. Anaesth., Vol. 36, 1964, pp. 563-571.

475. Meda, E. Riserche elettrocardiografiche darante la respirasione di miscele ricohe di ossigeno (Electrocardiographic research during the respiration of various oxygen concentrations). Riv. Med. Aeronaut., Vol. 13, 1950, pp. 441-454.

476. Michel, C.C., and F.F. Kao. Use of cross-circulation technique in studying respiratory responses to CO_2. J. Appl. Physiol., Vol. 19, 1964, pp. 1070-1074.

477. Michel, C.C., and J.S. Milledge. Respiratory regulation in man during acclimatization to high altitude. J. Physiol., London, Vol. 168, 1963, pp. 631-643.

478. Miller, H.C., and N.W. Smull. Further studies on the effects of hypoxia on the respiration of newborn infants. Pediatr., Vol. 16, 1955, pp. 93-103.

479. Mitchell, R.A. Cerebrospinal fluid and the regulation of respiration. In: Advances in Respiratory Physiology, Baltimore, 1955, pp. 1-47.

480. Mitchell, R.A., H.H. Loeschcke, J.W. Severinghaus, B.W. Richardson, and W.H. Massion. Regions of respiratory chemosensitivity on the surface of the medulla. Ann. N.Y. Acad. Sci., Vol. 109, 1963, pp. 661-681.

481. Mithoefer, J.H., and Kazemi. Effect of carbon dioxide on heart rate. J. Appl. Physiol., Vol. 19, 1964, pp. 1151-1156.

482. Mollaret, P., Vic-Dupont, J.J. Pocidalo, and J.F. Monsallier. Hyperbaric oxygenation. Presse Med., Vol. 73, 1965, pp. 777-783.

483. Mrosovsky, N., and A. Carr. Preference for light of short wavelengths in hatching gree sea turtles, *Chelonia mydas*, tested on their natural nesting beaches. behavior, Vol. 28, 1967, pp. 217-231.

484. Mullinax, P.F., and D.E. Beischer. Oxygen toxicity in aviation medicine. J. Aviat. Med., Vol. 29, 1958, pp. 660-670.

485. Murtz, R., and A.H. Begenat. Über die Wirkung hoher O_2-Partialdrucke auf die Respiration bei chronischer Hypoxämie (Effect of large O_2 partial pressures on the respiration for chronic hypoxia). Zschr. Ges. Exptl. Med., Vol. 139, 1965, pp. 166-167.

486. Nadel, J.A., and J.G. Widdicombe. Effect of changes in blood gas tensions and carotid sinus pressure on tracheal volume and total resistance to airflow. J. Physiol., London, Vol. 163, 1962, pp. 13-33.

487. —————————————————————— Reflex control of airway size. Ann. N.Y. Acad. Sci., Vol. 109, 1963, pp. 712-723.

488. Nakada, T., M. Kametaro, and N. Sumiro. Studies on the respiration responses during oxygen breathing. Lung a. Heart, Japan, Vol. 12, 1965, pp. 77-83.

489. Navratil, M., K. Kadlec, and S. Daum. Patophysiologie dychání (Breathing Pathophysiology). Praha, 1967.

490. Neil, E. The carotid glomus chemosensory mechanism. In: Regulation of Human Respiration. Oxford, 1961.

491. Nielsen, M., and H. Smith. Studies on the regulation of respiration in acute hypoxia. Acta Physiol. Scand., Vol. 24, 1951, pp. 293-313.

492. Nisell, O.G. The action of oxygen and carbon dioxide on the bronchioles and vessels in the isolated perfused lungs. Acta Physiol. Scand., Vol. 21, Suppl. 73, 1950.

493. Ohlsson, W.T.L. A study on oxygen toxicity at atmospheric pressure with special reference to the pathogenesis of pulmonary damage and clinical oxygen therapy. Acta Med. Scand., Vol. 128, Suppl. 190, 1948.

494. Opie, L.N., A.C. Smith, and J.M.K. Spalding. Conscious appreciation of the effect produced by independent changes of ventilation volume and of end-tidal P_{CO_2} in paralyzed patients. J. Physiol., London, Vol. 149, 1959, pp. 494-499.

495. Otey, E.S., and A.B. Otis. Hypocapnia as a stimulus to breathing during hypoxia. Federat. Proc., Vol 21, 1962, p. 448.

496. Otis, A.B., W.O. Fenn, and H. Rahn. Mechanics of breathing in man. J. Appl. Physiol., Vol. 2, 1950, pp. 592-607.

497. Paium, U., and W.E. Beckel. The carbon dioxide related behavior of the adults of *Orthosoma brunneum* (Forster), Canad. J. Zool., Vol. 42, 1964, pp. 295-304.

498. Paintal, A.S., and R.L. Riley. Responses of aortic chemoreceptors. J. Appl. Physiol., Vol. 21, 1966, pp. 543-548.

499. Pappenheimer, J.R., V. Fenol, and S.R. Heisey. Role of cerebral fluids as sutided in unanesthetized goats. Amer. J. Physiol., Vol. 208, 1965, pp. 436-450.

500. Partridge, R.S. Afferent impulses in the vagus nerve. J. Cell. Compar. Physiol., Vol. 2, 1933, pp. 367-380.

501. Pierce, E.C., C.J. Lambertsen, MJ. Strong, S.C. Alexander, and D. Steele. Blood P_{CO_2} and brain oxygenation at reduced ambient pressure. J. Appl. Physiol., Vol. 17, 1962, pp. 899-908.

502. Pi-Suñer, A. The regulation of the respiratory movement by peripheral chemoreceptors. Physiol. Revs., Vol. 27, 1947, pp. 1-38.

503. Priban, J.P. Central respiratory chemosensitivity and its relationship to peripheral nerve carbon dioxide sensitivity. Nature, Vol. 196, 1962, pp. 779-780.

504. Priban, J.P., and W.F. Fincham. Self-adaptive control and the respiratory system. Nature, Vol. 208, 1965, pp. 339-343.

505. Puccinelli, R., P. Mallet, J. Fabre, and P. Bouverot. Contribution a l'étude des atmosphères artificielles: réactions ventilatoires chez la chien éveillé soumis à une hypercapnie modérée en atmosphère normoxique (Contribution to the study of artificial atmospheres: ventilatory reactions for old dogs subjected to moderate hypercapnia in an oxygen atmosphere). Rev. Med. Aéronaut., Vol. 3, 1964, pp. 23-25.

506. Purves, M.J. The respiratory response of the new-born lamb to inhaled CO_2 with and without hypoxia. J. Physiol., London, Vol. 185, 1966, pp. 78-94.

507. Ramsay, A.G. Effects of metabolism and anesthesia on pulmonary ventilation. J. Appl. Physiol., Vol. 14, 1959, pp. 102-104.

508. Rankin, J., R.S. McNeil, and R.E. Forster. Influence of increased alveolar CO_2 tension on pulmonary diffusing capacity for CO_2 in man. J. Appl. Physiol., Vol. 15, 1960, pp. 543-549.

509. Read, D.J.C., J.E. Malone, and K.T. Fowler. Reproductibility of transient response to CO_2 inhalation in man. J. Appl. Physiol., Vol. 19, 1964, pp. 750-754.

510. Read, D.J.C., H. Simon, G. Brandi, and E.J.M. Campbell. Regulation of ventilation during rebreathing at imposed respiratory frequencies. Respirat. Physiol., Vol. 2, 1966-67, pp. 88-98.

511. Redderson, C.L., and J.S. Grawenstein. Untersuchungen über die Wirkung des Sauerstoffes und des Heliums auf den Kreislauf (Investigations on the effect of oxygen and helium on the circulatory system). Anaesthesist, Vol. 13, 1964, pp. 135-136.

512. Remmers, J.E., J.G. Brooks, and S.M. Tenney. Effect of controlled ventilation on the tolerable limit of hypercapnia. Respirat. Physiol., Vol. 4, 1968, pp. 78-90.

513. Richardson, D.W., H.A. Kontos, W.S. Shapiro, and J.L. Patterson. Role of hypocapnia in the circulatory responses to acute hypoxia in man. J. Appl. Physiol., Vol. 21, 1966, pp. 22-26.

514. Riley, R.L., R.E. Dutton, F.J.D. Fuleihan, S. Nath, H.H. Hurt, C. Yushimoto, J.H. Şipple, J. Permutt, and B. Bromberder-Barnea. Regulation of respiration and blood gases. Ann. N.Y. Acad. Sci., Vol. 109, 1963, pp. 829-850.

515. Riley, R.L., R.S. Ross, and B. Armstrong. Pulmonary arterial P_{CO_2} and ventilation in man. Federat. Proc., Vol. 20, 1961, p. 431.

516. Robert, M. Effets de l'inhalation d'oxygène sur débit et la fréquence cariaques et sur la pression artérielle systématique moyenne chez le chien narcotisé en normoxie (Effects of oxygen inhalation on the cardiac yield and frequency and on the systematic average arterial pressure in anesthetized dogs). Helv. Physiol. Pharmacol. Acta, Vol. 23, 1965, pp. 38-53.

517. Robertson, W.G., H.J. Left, V.S. Behar, and B.E. Welch. Observations on man in an oxygen-helium environment at 380 mm Hg total pressure. Aerosp. Med., Vol. 37, 1966, pp. 453-456.

518. Rosenthal, J. Die Atembewegungen in ihren Beziehungen zum Nervus vagus (Respiratory motion and its relationship to the vagus nerve). Berlin, 1862.

519. Rosenfeld, M., and F.F. Snyder. Stages of development of respiratory regulation and changes ccurring at birth. Amer. J. Physiol., Vol. 121, 1938, pp. 242-249.

520. Said, S.J., and C.M. Banerjee. Venous admixture to the pulmonary circulation in human subjects breathing 100% oxygen. J. Clin. Investg., Vol. 42, 1963, pp. 507-515.

520a Said, S.J., P.K. Davis, and J.L. Crosier. Continuous recording in vivo of arterial blood P_{O_2} in dogs and man. J. Appl. Physiol, Vol. 16, 1961, pp. 1129-1132.

521. Saito, K., Y. Honda, and N. Hasumura. Ventilatory response to hypoxia at normal arterial pH and P_{CO_2} in dogs. Japan. J. Physiol., Vol. 10, 1960, pp. 631-681.

522. Salzona, J., and F.G. Hall. Effect of hypothermia on ventilatory response to carbon dioxide inhalation and carbon dioxide infusion in dogs. J. Appl. Physiol., Vol. 15, 1960, pp. 397-402.

523. ——————————————————— Influence of arterial oxygen tension on apneic threshold for CO_2 in normothermic and hypothermic dogs. Biol. Abstr., Vol. 47, No. 65401, 1965.

524. Samaan, A., and G. Stella. The response of the chemical receptors of the carotid sinus to the pressure of CO_2 in the arterial blood in the cat. J. Physiol., London, Vol. 85, 1935, pp. 309-319.

525. Samanek, M., and D.M. Aviado. Interrelationship between pulmonary blood flow and bronchomotor tone: P_{O_2} and P_{CO_2}. J. Appl. Physiol., Vol. 22, 1967, pp. 719-730.

526. Schaefer, K.E. A concept of triple tolerance limits based on chronic carbon dioxide toxicity studies. Aerosp. Med., Vol. 32, 1961, pp. 197-204.

527. Schilder, D.R., A. Roberts, and D.L. Fry. Effects of gas density and viscosity on the maximal expiratory flow-volume relationship. J. Clin. Investig., Vol. 42, 1963, pp. 1705-1713.

528. Schiller, J., F. Lowell, M. Lynch, and W. Franclin. The effect of helium oxygen mixtures in pulmonary function on asthmatic patients. J. Allergy, Boston, Vol. 26, 1955, pp. 11-15.

529. Schmidt, C.F. Respiration. In: Medical Phsyiology. St. Louis, 1956.

530. Schmidt, C.F., and J.H. Comroe. Functions of the carotid and aortic bodies. Phytiol. Revs., Vol. 20, 1940, pp. 115-157.

531. Schreuder, O.B. Medical aspects of aircraft pilot fatigue with special reference to the commerical jet pilot. Aerosp. Med., Vol. 37. 1966, pp. 1-43.

532. Schnuurmans Stekhoven, J.H., and F. Kreuzer. Alveolar-arterial O_2 and CO_2 pressure differences in the anesthetized, artificially ventilated dog. Respirat. Physiol., Vol. 3, 1967, pp. 177-191.

533. Schwieler, G.H. Some aspects of respiratory regulation during the post-natal development in cats and rabbits. Life Sci., Vol. 6, 1967, pp. 1803-1810.

534. Sechzer, PH., L.D. Egbert, H.W. Linde, D.Y. Cooper, R.D. Dripps, and H.L. Price. Effect of CO_2 inhalation on arterial pressure, EEG and plasma catecholamines and 17-OH corticosteroids in normal man. J. Appl. Physiol., Vol. 15, 1950, pp. 454-458.

535. Semple, S.J.G. Respiration and cerebrospinal fluid. Brit. J. Anaesth., Vol. 37, 1965, pp. 262-267.

536. Seto, H. Über zwischen Aorta und Arteria pulmonalis gelegene Herzparaganglien (The heart paraganglia located between the aorta and the pulmonary artery). Zschr. Zellforsch., Vol. 22, 1935, pp. 213-231.

537. Siri, W.E., D.C. VanDyke, H.S. Winchell, M. Pollicove, H.G. Parker, and A.S. Cleveland. Early crythropoietin, blood and physiological responses to severe hypoxia in man. J. Appl. Physiol., Vol. 21, 1966, pp. 73-80.

538. Smith, C.A. The physiology of the newborn infant. Oxford, 1959.

539. Sommers, P. van, Oxygen-motivated behavior of the goldfish, *Carassium auratus*. Science, Vol. 137, 1962, pp. 678-679.

540. ————————— Behavioral regulation of the respiratory environment in three vertebrate species. Harvard University, 1962.

541. —————————. Air-motivated behavior in the turtle. J. Compar. Physiol. Psychol., Vol. 56, 1963, pp. 590-596.

542. —————————. Carbon dioxide escape and avoidance behavior in the brown rat. J. Compar. Physiol. Psychol., Vol. 56, 1963, pp. 584-589.

543. Stegemann, J., and D. Böning. Die Wirkung erhöhter Metabolikonzentrationen in Muskel auf die Ventilation (The effect of increased metabolite concentrations in muscles on ventilation). Pflügers Arch., Vol. 294, 1967, pp. 214-222.

544. Strumza, M.V. L'hyperventilation hypoxique facteur limitatif d'hypercapnie exogène (Hypoxic hyperventilation as a limiting factor of exogenic hypercapnia). Rev. Med. Aéronaut., Vol. 3, 1964, pp. 589-592.

545. —————————. Sur le méchanisme de l'atténuation de l'hypoxie hypoxique par l'enrichissement en CO_2 de l'air inspiré (The attenuation mechanism of hypoxic hypoxia due to CO_2 enrichment in inhaled air). Compt. Rend. Acad. Sci., D262, Vol. 16, 1966, pp. 1740-1741.

546. Tenney, S.M. Concepts of threshold and sensitivity of ventilatory control. Ann. N.Y. Acad. Sci., Vol. 109, 1963, pp. 634-648.

547. Tenney, S.M., and J.G. Brooks. Carotid bodies stimulus interaction and ventilatory control in unanesthetized goats. Respirat. Physiol., Vol. 1, 1966, pp. 211-224.

548. Tinel, J. Régulation de la circulation cérébrale à l'inhalation d'oxygène (Regulation of cerebral circulation by inhalation of oxygen). Compt. Rend. Sci. Soc. Biol., Vol. 96, 1927, p. 665.

549. Tribukait, B. Experimentelle Untersuchungen zur Regulation der Erythropoiese unter besonderer Berücksichtigung der Bedeutung des Sauerstoffs (Experimental investigations of the regulation of erythropsia with special consideration of the importance of oxygen). Acta Physiol. Scand., Vol. 58, Suppl. 208, 1963.

550. ——————— Die Readaptation der höhenpolyzytämischen Ratte am Meereshöhe (The readaptation of rats afflicted with altitude polycthemia to sea level conditions). Acta Physiol. Scand., Vol. 57, 1963, pp. 419-430.

551. Van Liew, H.D. Subcutaneous tissue P_{O_2} and P_{CO_2} of rats in a high CO_2 atmosphere. Aerosp. Med., Vol. 34, 1963, pp. 499-500.

552. Vogel, J.A., and A. Harris. Cardiopulmonary responses of resting man during early exposure to high altitude. J. Appl. Physiol., Vol. 22, 1967, pp. 1124-1128.

553. Wayne, H.H. Clinical differentiation between hypoxia and hyperventilation. J. Aviat. Med., Vol. 29, 1958, pp. 307-315.

554. Weidman, W.H., J.L. Titus, and J.T. Shephard. Effect of chronic hypoxia on the pulmonary circulation of cats. Proc. Soc. Exptl. Biol. Med., Vol. 118, 1965, pp. 1158-1164.

555. Weistein, S.A. Carbon dioxide as a reinforcer in escape conditioning. Cond. Reflex, Vol. 2, 1967, pp. 118-126.

556. Wett, D., L. Katz, and L. Kohn. Respiratory failure following denervation of the carotid sinus region. Amer. J. Physiol., Vol. 107, 1934, pp. 213-220.

557. White, C.S., and O.O. Benson. Physics and Medicine of the Upper Atmosphere. Univ. New Mexico Press, 1952.

558. Whitenberger, J.L. Effects of atmospheric factors on the mechanics of breathing. In: Man's Dependence on Earthly Atmosphere. N.Y., 1962, pp. 257-261.

559. Wiemer, W., and P. Kiwull. Die interferenz zentraler und peripherer Mechanismen bei der chemischen Steuerung der Atmung (The interference of central and peripheral mechanisms in the chemical control of respiration). Acta Neuroveget., Vol. 28, 1966, pp. 289-312.

560. Wiemer, W., N. Ott, and H. Winterstein. Reflektorische und zentrale Anteile der O_2-Mangel- und CO_2-Hyperpnoe des Kaninchens (Reflector and central components of the O_2 deficiency and CO_2 hyperpnea of rabbits). Zschr. Biol., Vol. 114, 1963, pp. 230-234.

561. Wiley, R.L., and F.W. Zechman. Perception of added airflow resistance in humans. Respirat. Physiol., Vol. 2, 1966/67, pp. 73-87.

562. Wilhjelm, B.J. Protective action of carbon dioxide against anoxia with and without anaesthesia. Acta Pharmacol. Coxic, Vol. 24, 1966, pp. 355-362.

563. Winter, C.W. Combination of hypoxic and hypercapnic stimulation at the carotid body. Amer. J. Physiol., Vol. 136, 1942, pp. 200-206.

564. Winterstein, H. Die reaktionstheorie der Atmungsregulation (The reaction theory of respiration regulation). Pflügers Arch., Vol. 187, 1921, pp. 293-298.

565. —————————. Probleme der Atmungsfunktion im Lichte neuerer Forschung (Problems of respiration in view of recent research). Pflügers Arch., Vol. 268, 1958, pp. 16-17.

566. Winterstein, H., and W. Wiemer. Die Wirkung von Lobelin und Natriumzyanid bei suboccipitaler Injektion (The effect of Lobeline and Sodium cyanide for suboccipital injection). Arch. Exptl. Pathol. Pharmac., Vol. 235, 1959, pp. 235-245.

567. Witzleb, E. Über temperaturabhängige Aktionspotentiale im Carotissinusnerven (The temperature-dependent action potentials in the carotis sinus nerve). Pflügers Arch., Vol. 255, 1952, pp. 181-188.

568. Womack, G.J. Evidence for the cerebral vasoconstrictor effect of breathing 100% oxygen. Aerosp. Med., Vol. 32, 1961, pp. 328-333.

569. Wood, W.B., and L.H. Leve. Ventilatory dynamics under hyperbaric states. Arch. Environm. Health., Vol. 7, 1963, pp. 47-59.

570. Wright, R.A., M.A. Lesser, and H.S. Weiss. Metabolism and X-Ray sensitivity of chick embryos incubated in a helium-oxygen atmosphere. Aerosp. Med., Vol. 35, 1964, pp. 284-290.

571. Yadzu, K. Clinical pathophysiological studies on age difference of respiratory regulation in low oxygen inhalation. Japan. Circulat. J., Vol. 29, 1965, pp. 592-594.

572. Yamamoto, W.S. Ventilatory responses of rats to electrical stimulation in CO_2-containing atmospheres. Amer. J. Physiol., Vol. 191, 1957, pp. 423-428.

573. Yamamoto, W.S., and M.W. Edwards. Homeostasis of carbon dioxide during intravenous infusion of CO_2. J. Appl. Physiol., Vol. 15, 1960, pp. 807-815.

574. Yamamoto, W.S., and W.F. Raub. Models of the regulation of external respiration in mammals. Comp. Biomed. Res., Vol. 1, 1967, pp. 65-104.

575. Ypersele, van de, Stihou, P.F. Gúlyassy, and W.B. Schwarts. Effects of chronic hypercapnia on electrolyte and acid-base equilibrium. J. Clin. Investig., Vol. 41, 1962, pp. 2246-2253.

576. Zotterman, Y. Action potentials in the glossophyarngeal nerve and in the chorda tympani. Scand. Arch. Physiol., Vol. 72, 1935, pp. 73-77.

577. Zuntz, W., and J. Gepptert. Über die Natur der normalen Atemreize und und der Ort ihrer Wirkung (The nature of normal respiration stimuli and the location where they are effective). Pflügers Arch., Vol. 38, 1886, pp. 337-338.

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